

Celiac Disease

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Celiac Sprue/ Gluten-Sensitive Enteropathy/Celiac Disease/ Non-Tropical Sprue

- **The most common food intolerance in Western populations**
- **A chronic small intestinal enteropathy triggered by gluten proteins from wheat, barley, and rye**
- **Characterized by an autoimmune response in genetically susceptible individuals resulting in small intestinal injury and systemic symptoms**
- **Withdrawal of gluten usually leads to prompt symptom improvement & eventual healing of mucosal damage**

Celiac Disease

- **First described by Samuel Gee in 1888: “On the Coeliac Affection”**
- **Clinical recognition of celiac-like malabsorptive disease dates back to the first century AD**
- **The cause of CD unexplained until WWII**
 - **Dutch pediatrician, Willem K. Dicke, noted clinical improvement in affected children during periods of food shortages when bread was in short supply**
 - **Symptoms recurred when bread was reintroduced after the war.**
- **Controlled experiments by Dr Dicke, et al, after WWII determined that celiac disease was triggered by proteins in three “toxic cereals”: wheat, barley, and rye**

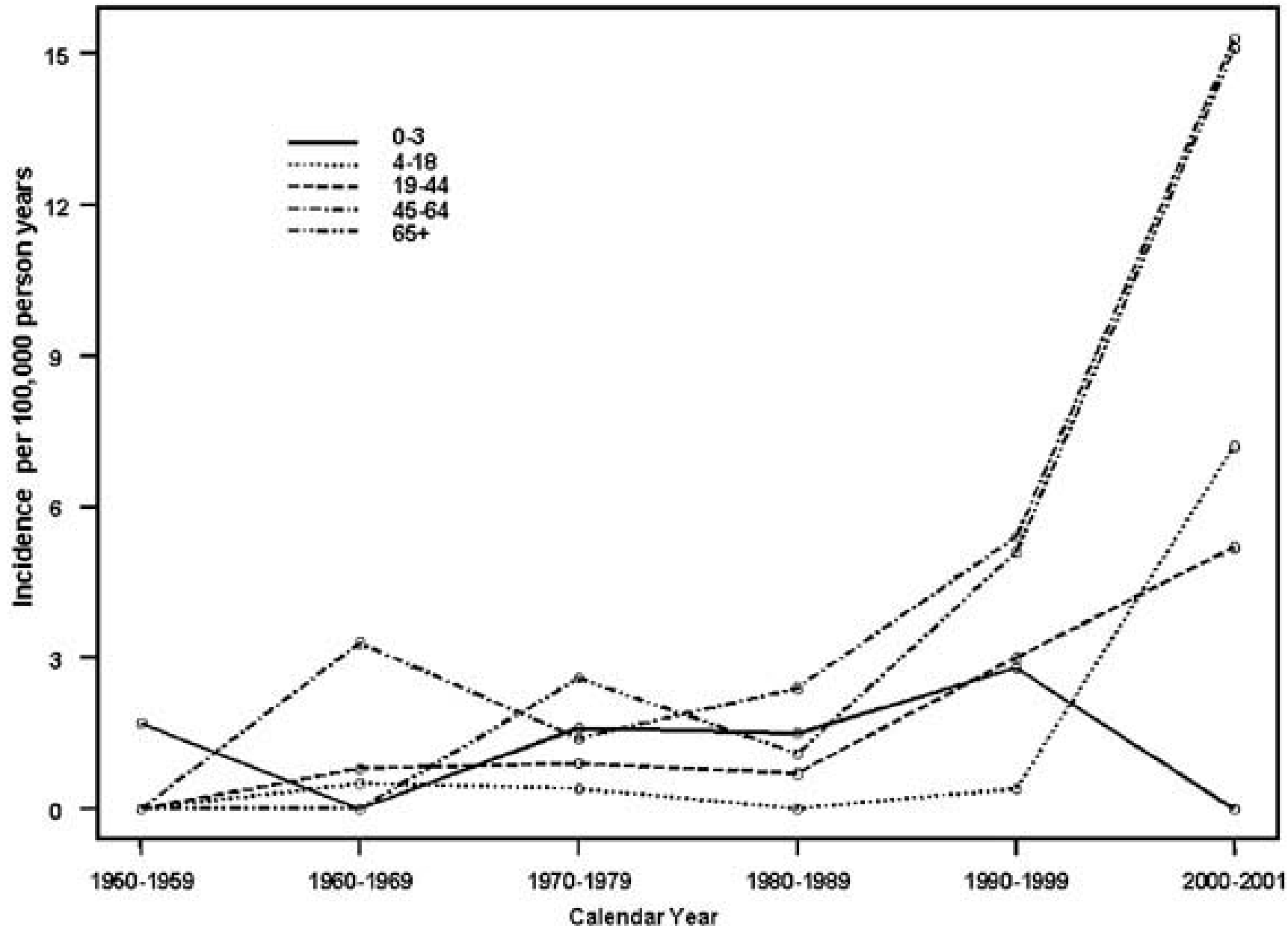
Epidemiology

- The true prevalence of CD is difficult to estimate since the majority of cases are have atypical, minimal, or no GI symptoms
- The highest prevalence is in Western Europe (0.3-1.0%) and countries to which Europeans migrated (Australia and North America)
- Prevalence rates similar to Europe have been found in Saharan Africa, and the Middle East especially Iran, Pakistan and Northern India
- Reported in all races but very rare among pure Chinese, Japanese, and Afro-Caribbean

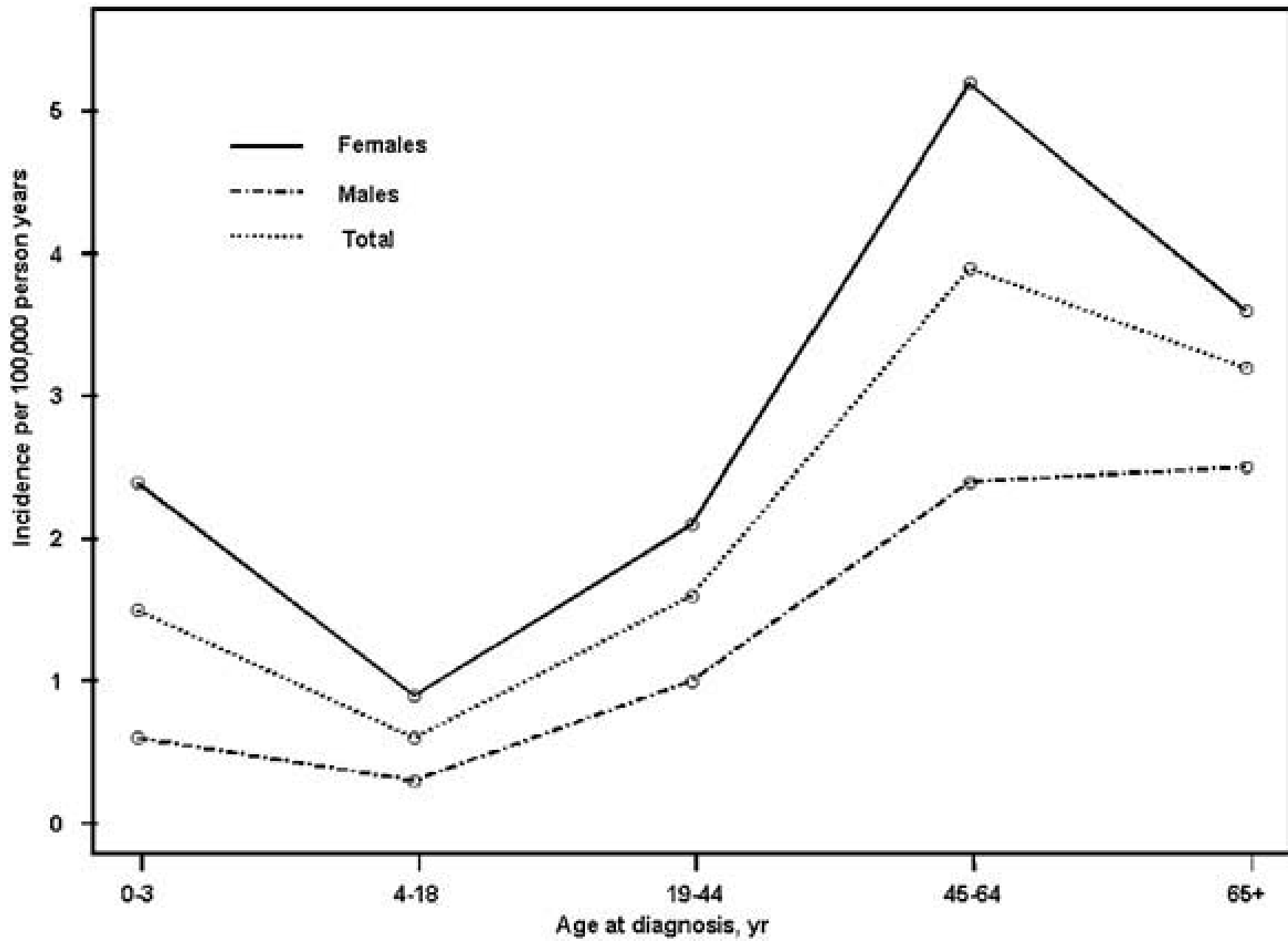
Epidemiology

- The incidence of *diagnosed* CD in the US has increased 10 fold between 1950 and 2000
- 18 large, population-based screening studies based on AEA indicate a prevalence of celiac disease in the USA of 0.5-1.26%, or approximate 3 million Americans
- The mean age of diagnosis is 46.4 years
- 20% diagnosed after age 60

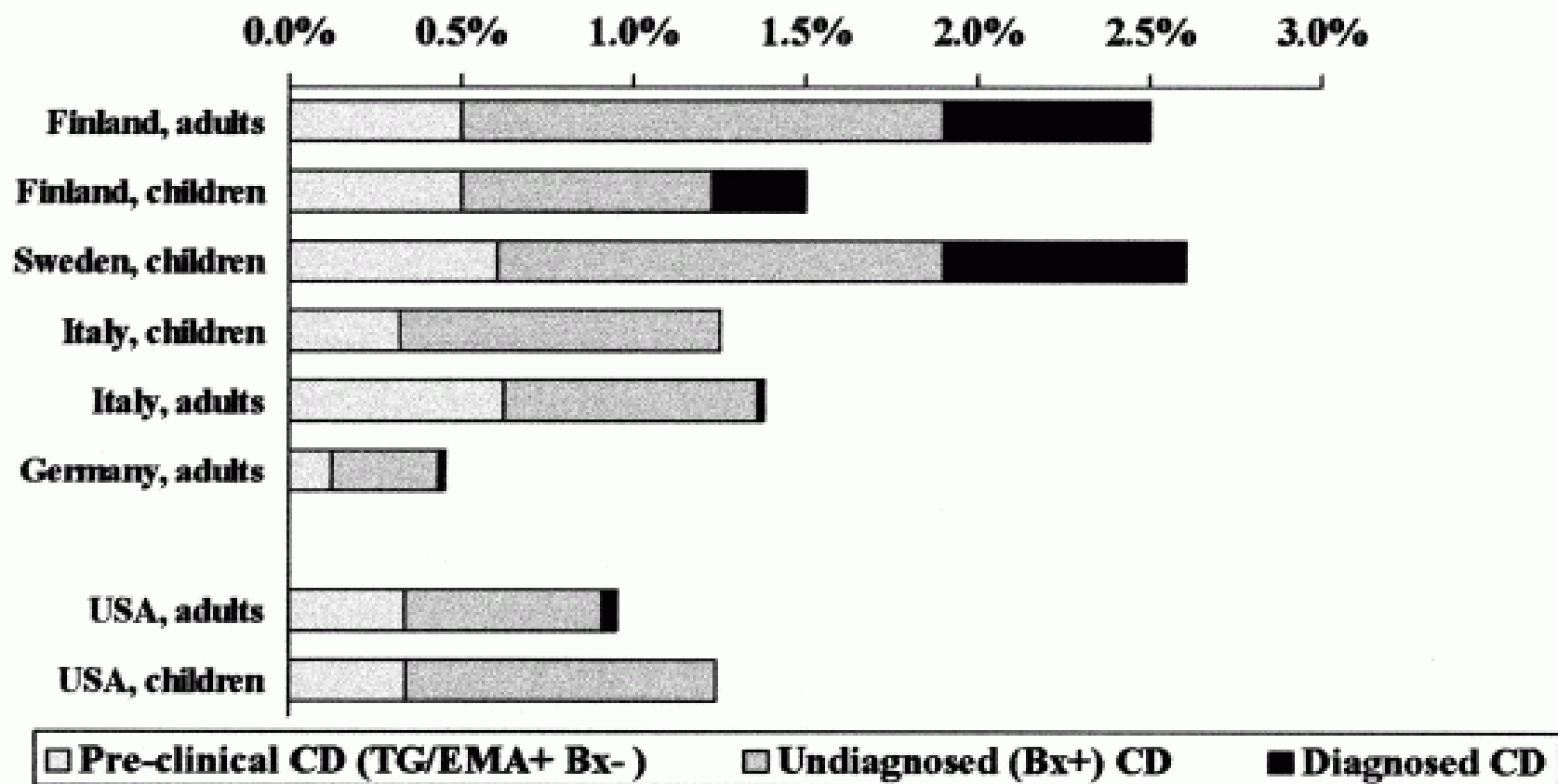
Mayo Clinic CD Trends 1950-2001



Mayo Clinic CD Trends 1950-2001



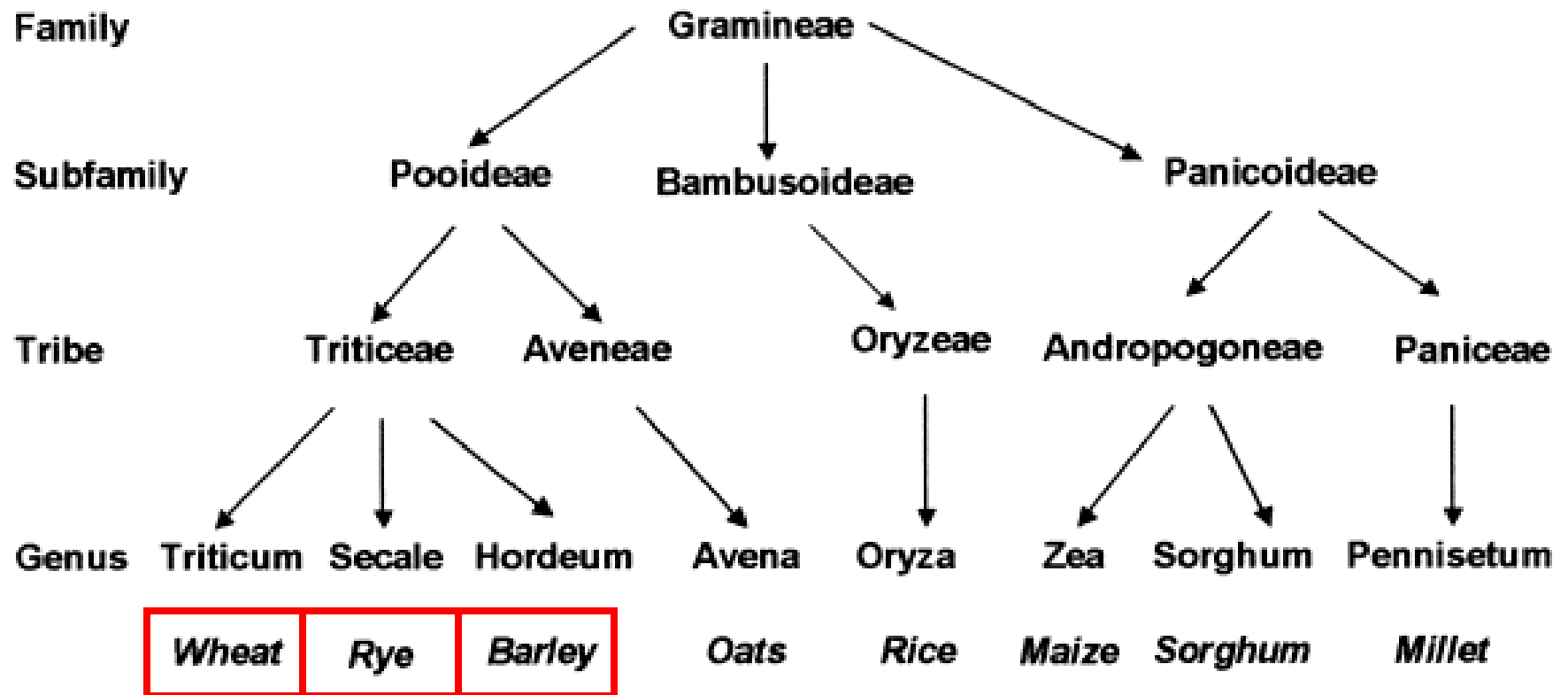
Prevalence



**90-99% of Patients with Celiac
Disease in the US may be
Undiagnosed**

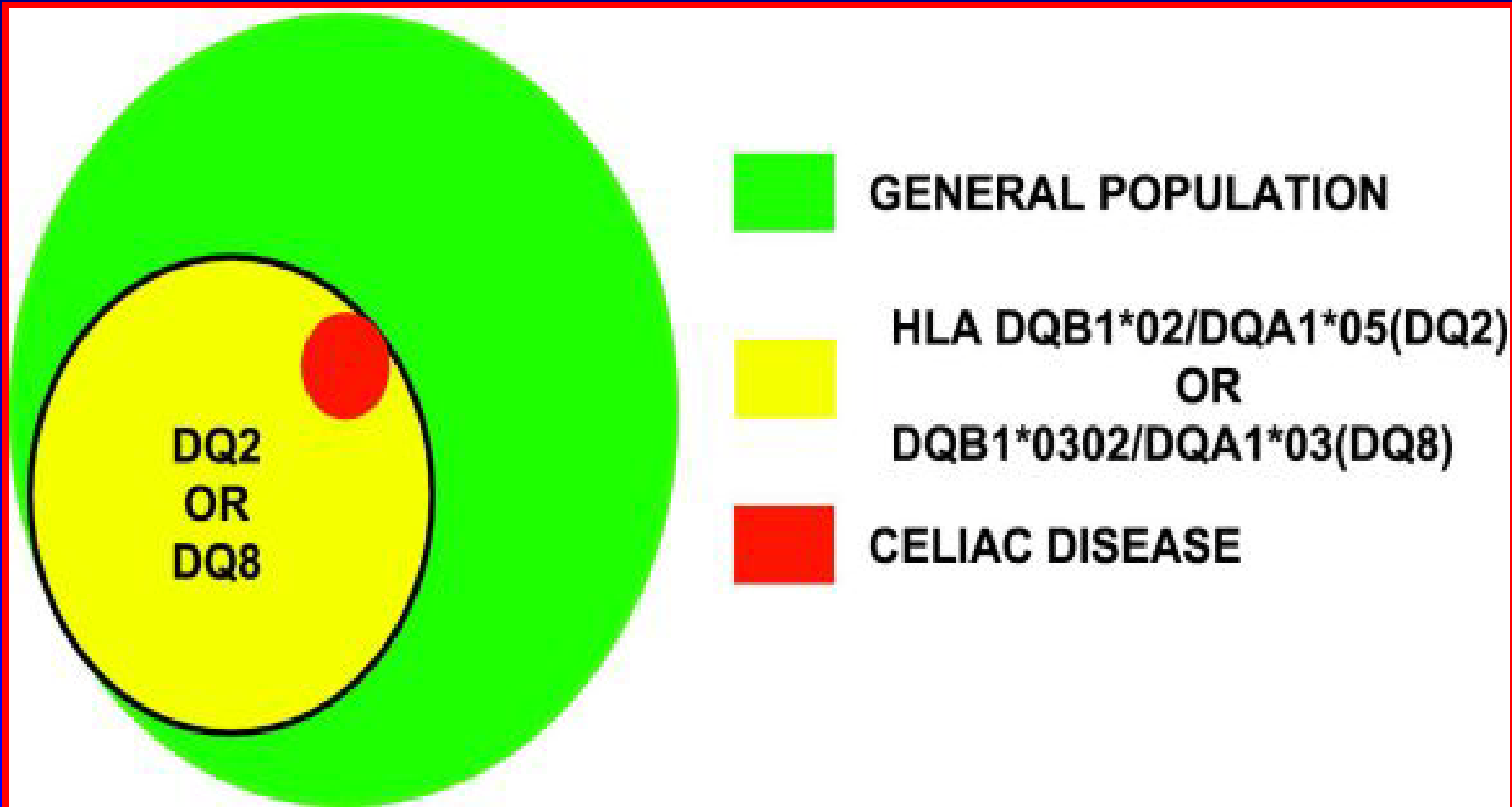
Celiac Disease: Pathogenesis

Taxonomy of Dietary Grains



Pathophysiology

- HLA genetics play a key role in pathogenesis
- 5-15% prevalence in first-degree relatives and 70-75% concordance in monozygotic twins
- HLA-DQ2 and/or HLA-DQ8 present in 95% of affected individuals vs 30% of general population
- HLA-DQ2 and-DQ8 are HLA class II molecules that bind and present peptides to CD4-positive T cells
- Intestinal antigen-presenting cells with the DQ2 or DQ8 alleles have a high affinity for negatively charged amino acids in bound proteins

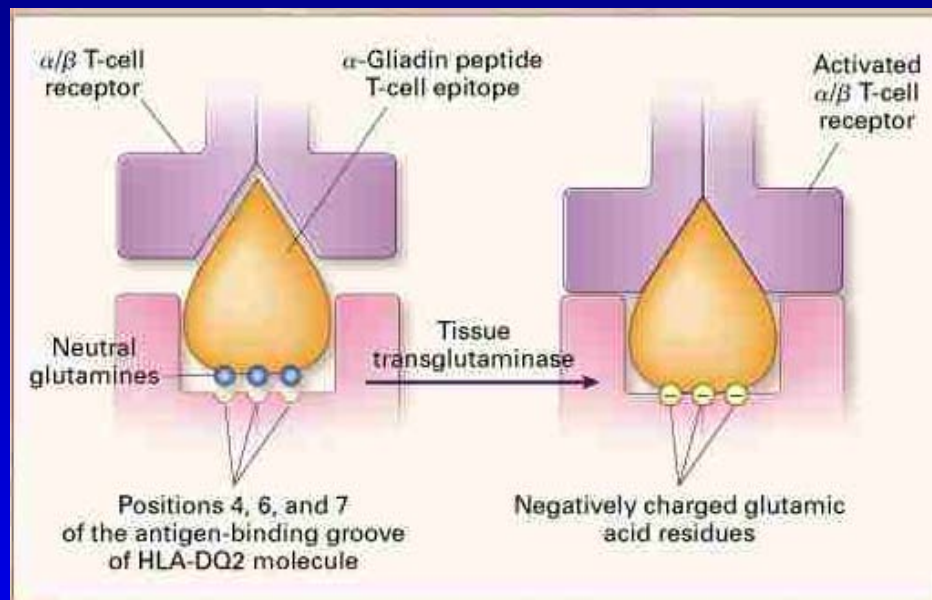
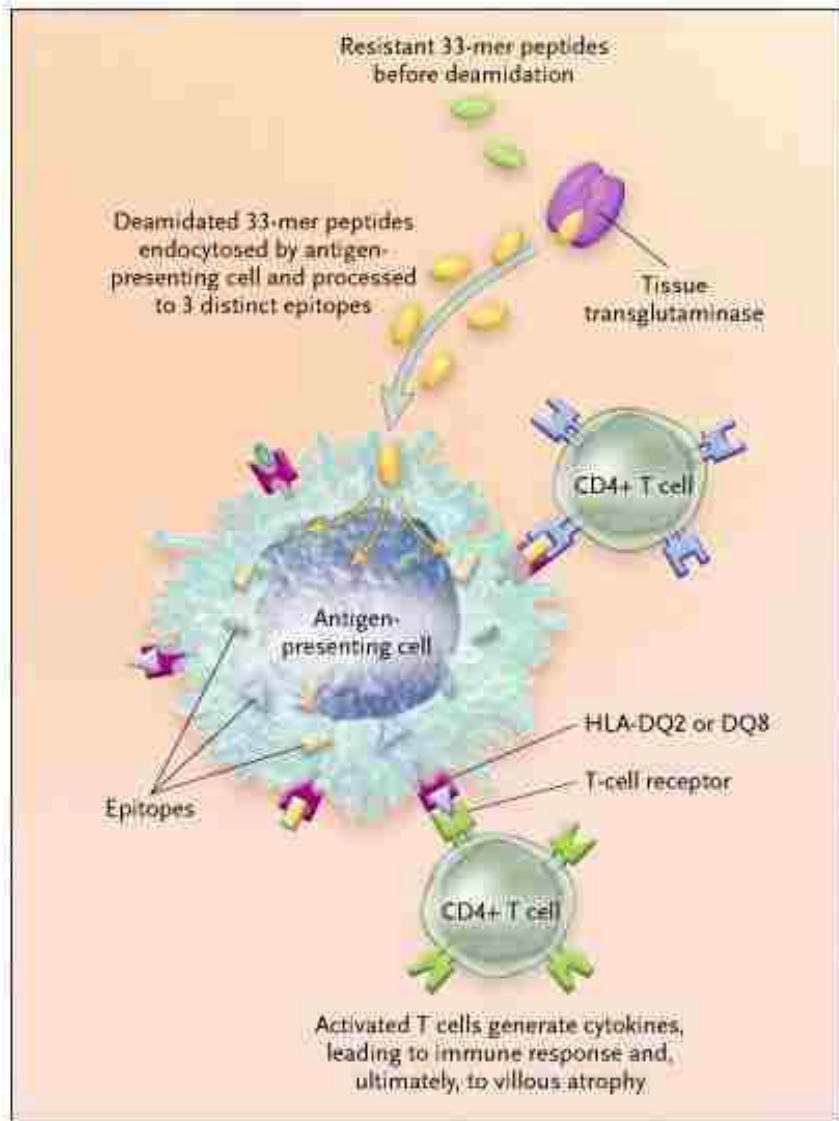


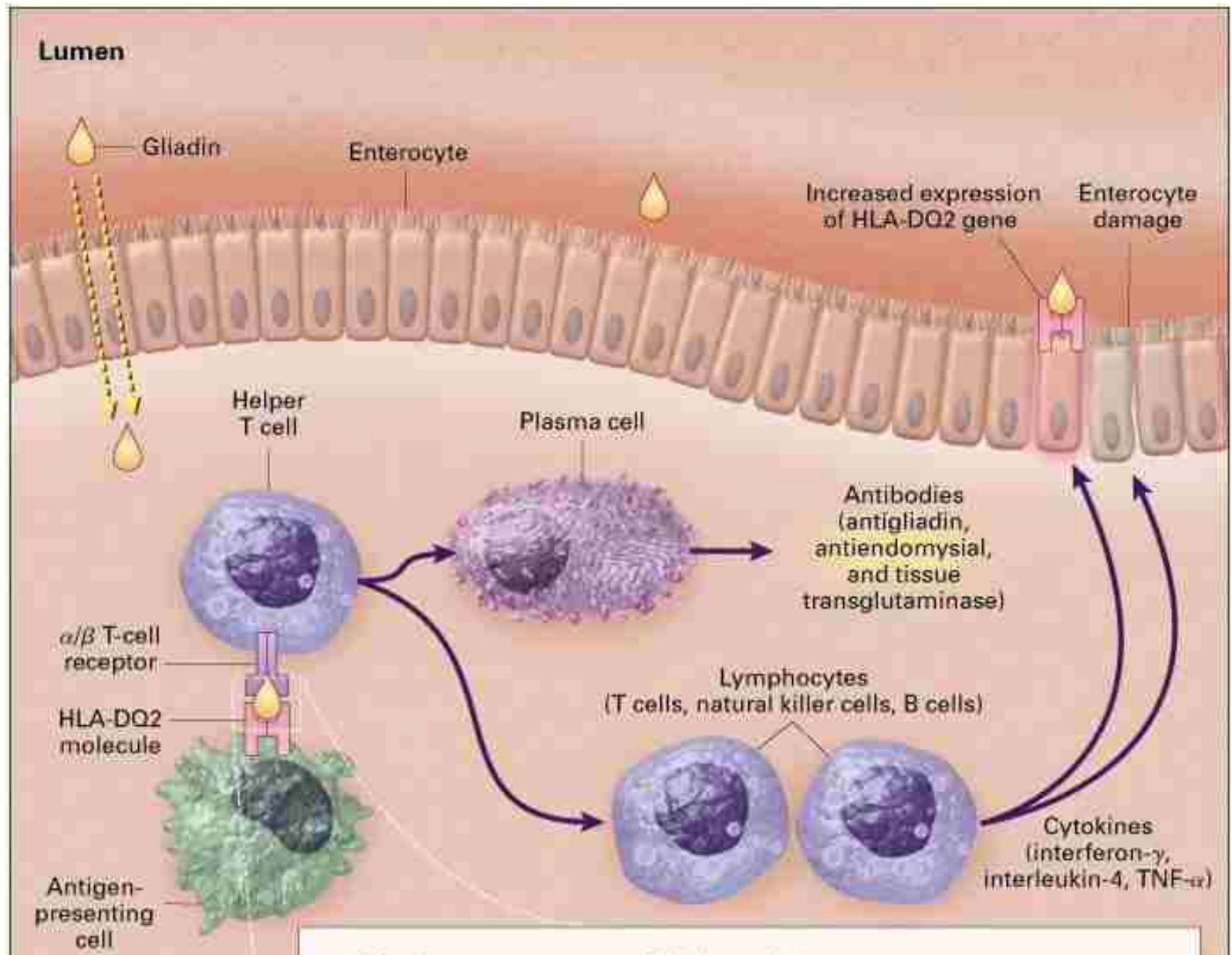
Pathogenesis of Celiac Disease

- Wheat, rye, and barley contain an alcohol-extractable disease-activating protein component termed gluten
- “Gluten” is a complex mixture of hundreds of related but distinct proteins
- Gluten is a mixture of two protein families: gliadin and glutenin both of which can trigger a toxic T-cell response
- Gluten proteins have extraordinary levels of proline and glutamine

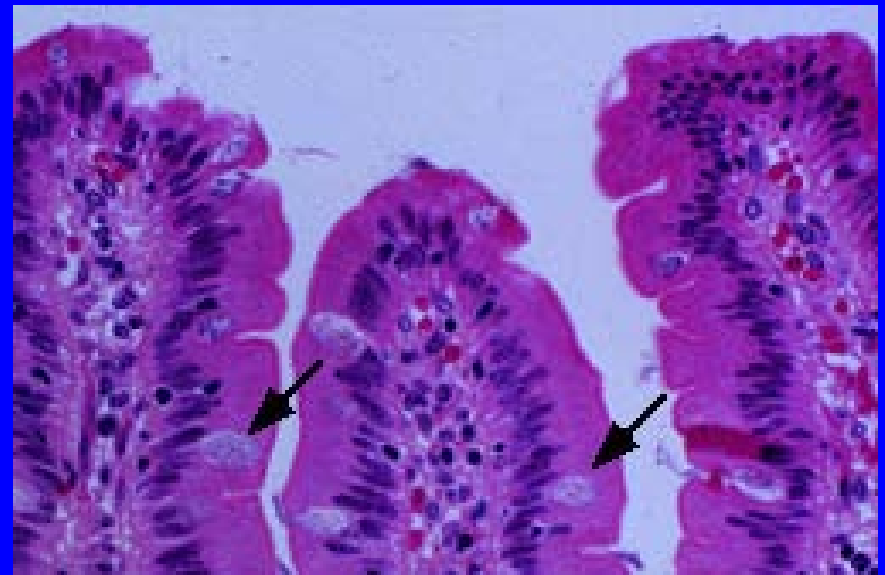
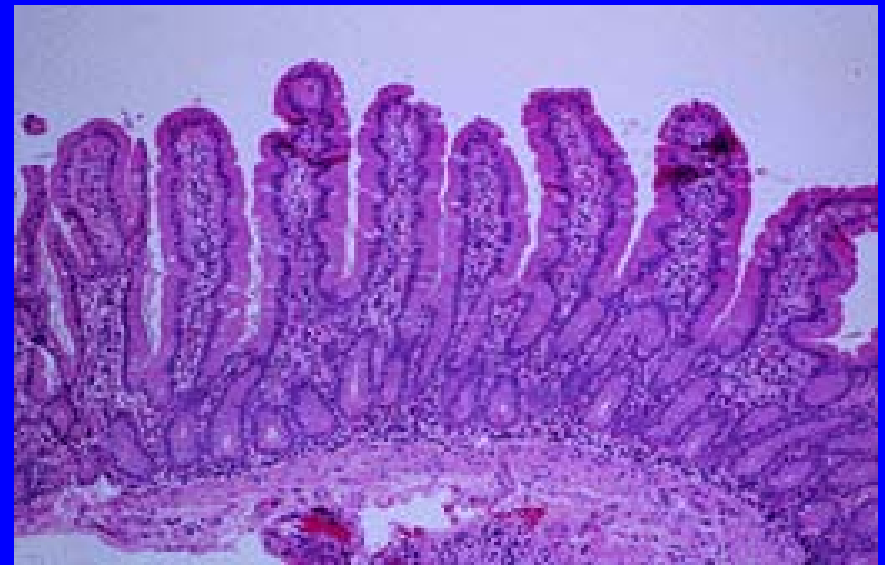
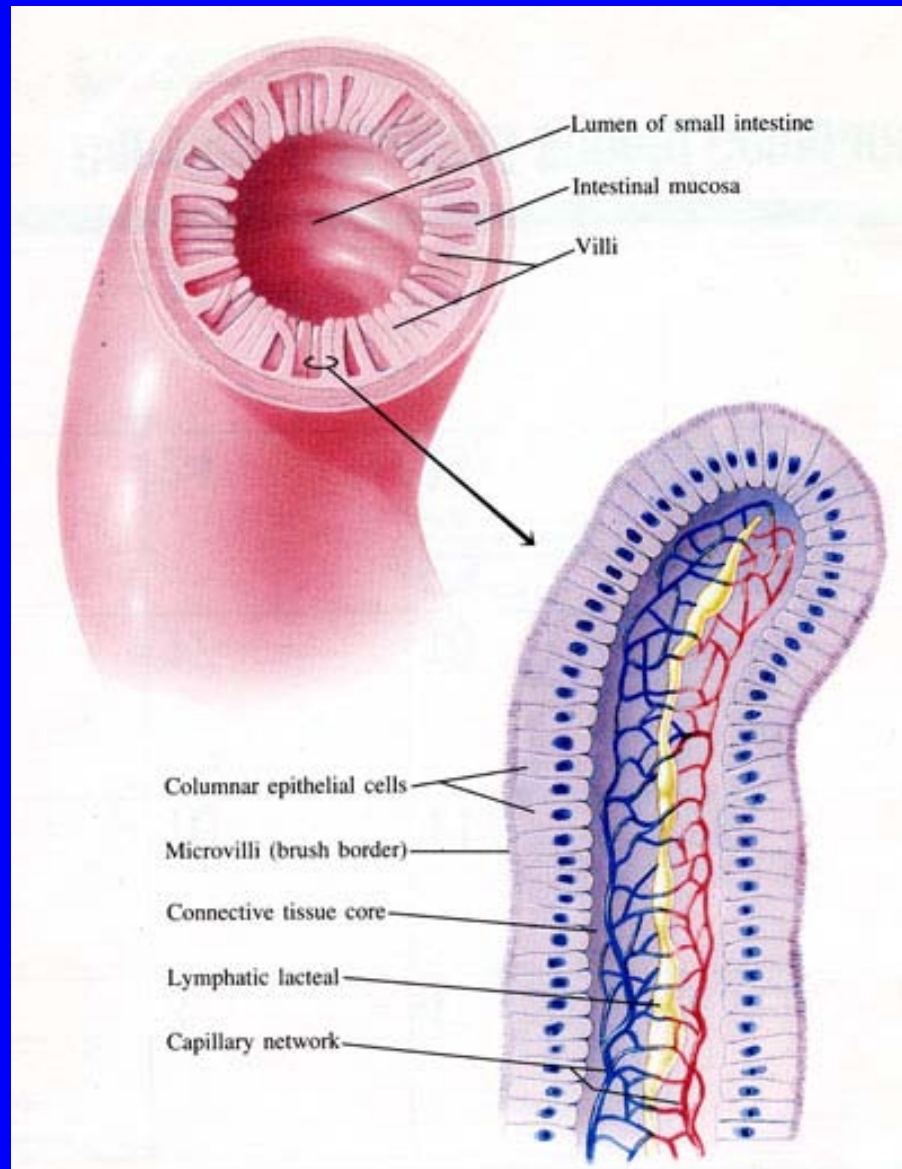
Pathogenesis of Celiac Disease

- The high proline content of glutens renders these proteins resistant to proteolytic digestion by gastric, pancreatic, or brush border enzymes.
- An intact 33- amino acid peptide (residues 55-88) results from this incomplete enzymatic digestion
- Tissue transglutimase (tTG), the target auto-antigen of anti-endomycial antibodies, is a ubiquitous enzyme released by endothelial cells, fibroblasts in response to inflammation
- TTG deaminates the glutamine residues into negatively charged glutamic acid residues increasing binding to HLA-DQ2 and DQ8

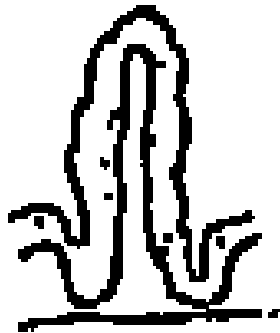




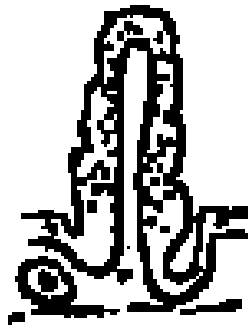
Structure of the Intestinal Villous



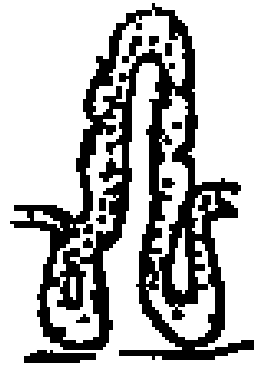
Histologic Grades of Celiac Disease: Marsh Classification



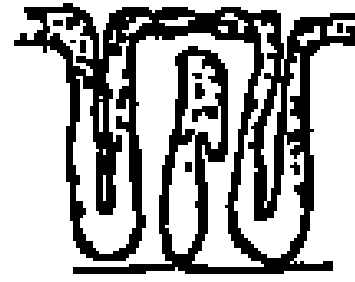
Marsh I



Marsh II



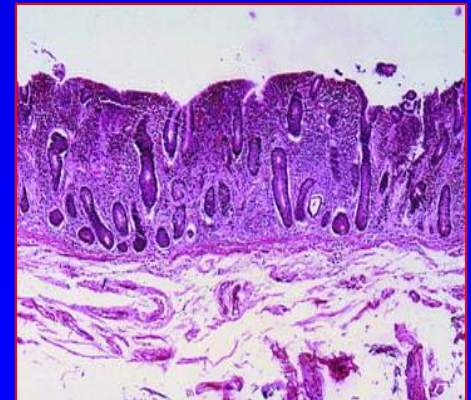
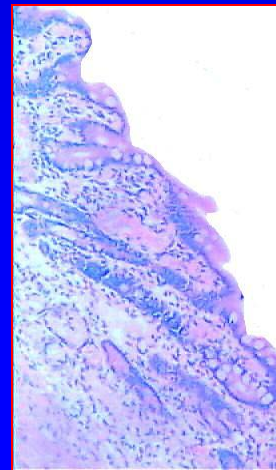
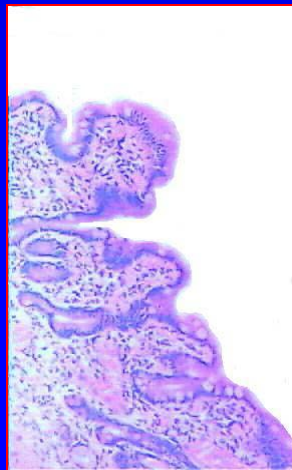
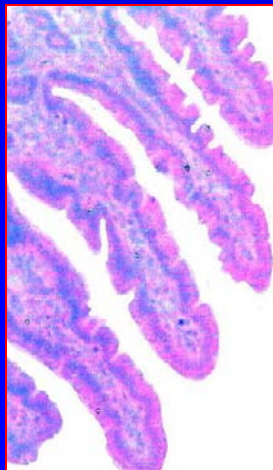
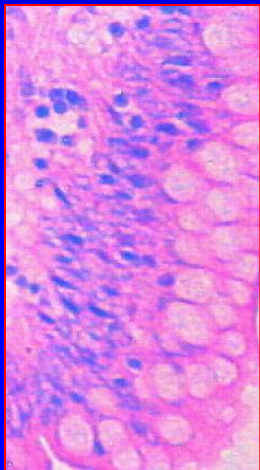
Marsh IIIa
Partial VA



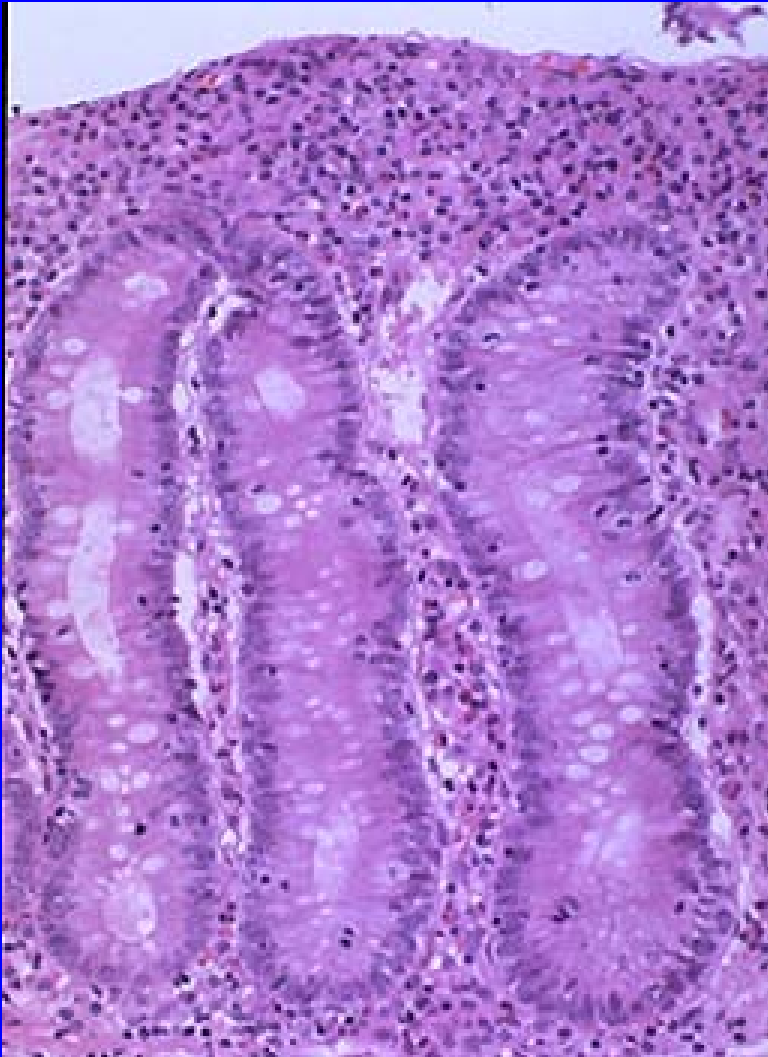
Marsh IIIb
Subtotal VA



Marsh IIIc
Total VA



Total Villous Atrophy



Pathophysiology

- **There is a gradient of severity of disease from the duodenum (most severe) to the distal intestine**
- **Length of small intestine involved and severity of mucosal injury varies from patient to patient**
- **The small intestine has considerable functional reserve so the severity of the proximal mucosal changes do not necessarily correlate with the severity of clinical symptoms.**

Clinical Manifestations of Celiac Disease

Clinical Presentation

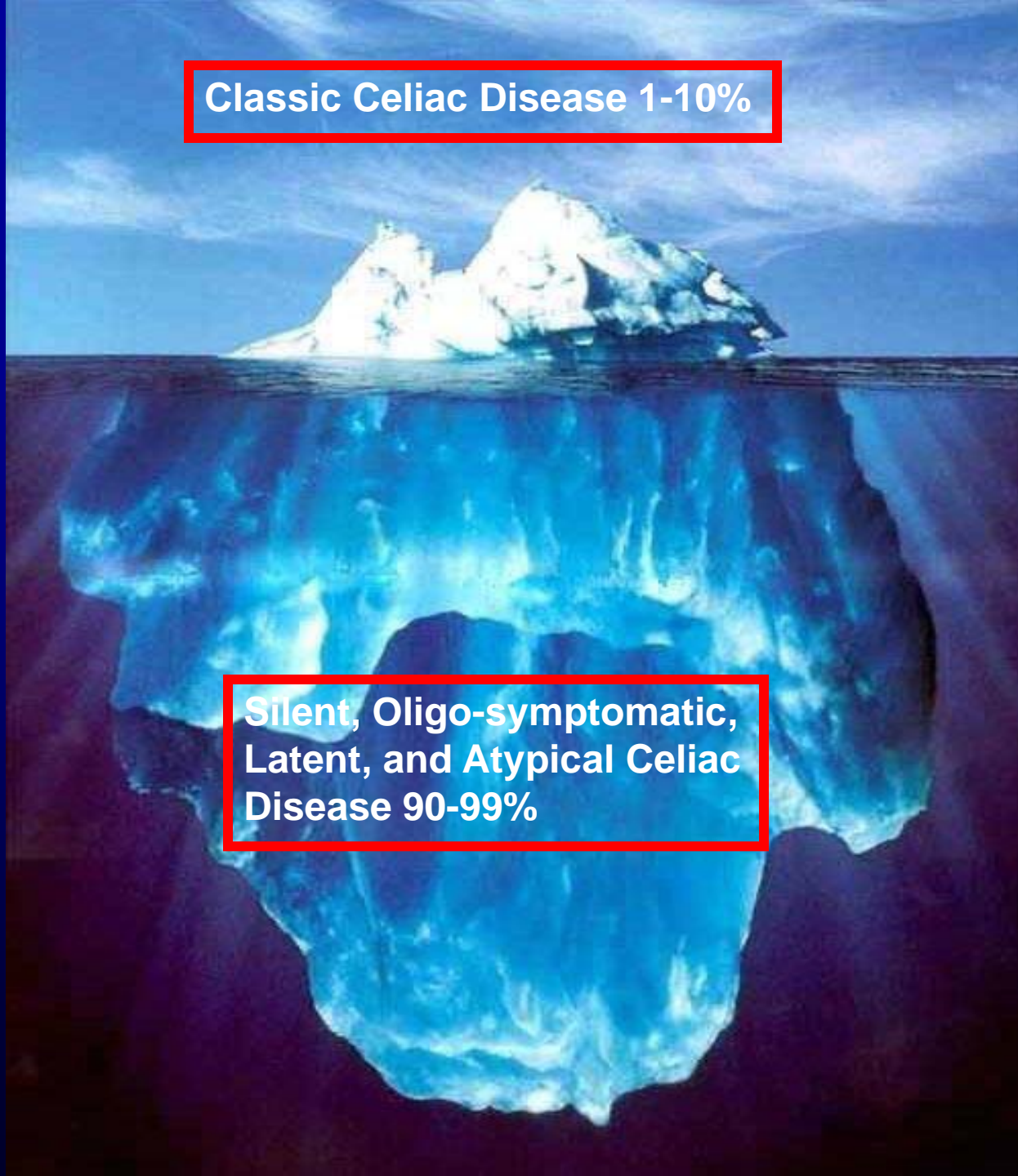
- Celiac disease is an autoimmune disease with highly variable clinical expression, potentially affecting multiple organ systems
- Estimates that $>2/3$ have no or minimal GI symptoms (Silent and Latent CD)
- Others may present in atypical fashion such as unexplained iron deficiency, abnormal liver function, IBS
- The mean delay between onset of symptoms and diagnosis is 4.4 years
 - The mean age of diagnosis is 46.4 years
 - 20% diagnosed after age 60

Classification of Celiac Disease

- **Classic Celiac Disease**
 - Villous atrophy
 - Symptomatic malabsorption
 - Resolution on a gluten-free diet
- **CD with Non-classic Symptoms**
- **Silent Celiac:** EMA(+) /Villous atrophy without symptoms
- **Latent Celiac:** EMA(+)/ normal mucosa
 - Normal mucosa at earlier age with classic disease later in life
 - Classic disease in childhood with remission in adult life on gluten-free diet

Classic Celiac Disease 1-10%

**Silent, Oligo-symptomatic,
Latent, and Atypical Celiac
Disease 90-99%**



Classic CD Manifestations

- **Malabsorption**
 - Diarrhea
 - Flatulence/bloating/distension
 - Weight Loss
 - Abdominal pain
 - Anorexia
- **Iron deficiency anemia**
- **Osteopenia**

Dominant Symptoms in Adult CD Patients Diagnosed 2000-2001 Mayo Clinic

- **Anemia 38%**
- **Diarrhea 33%**
- **Abdominal Pain 33%**
- **Bloating 33%**
- **Nausea/Vomiting 19%**
- **Weight Loss 14% (27% overweight)**
- **Flatulence 14%**
- **Steatorrhea 10%**

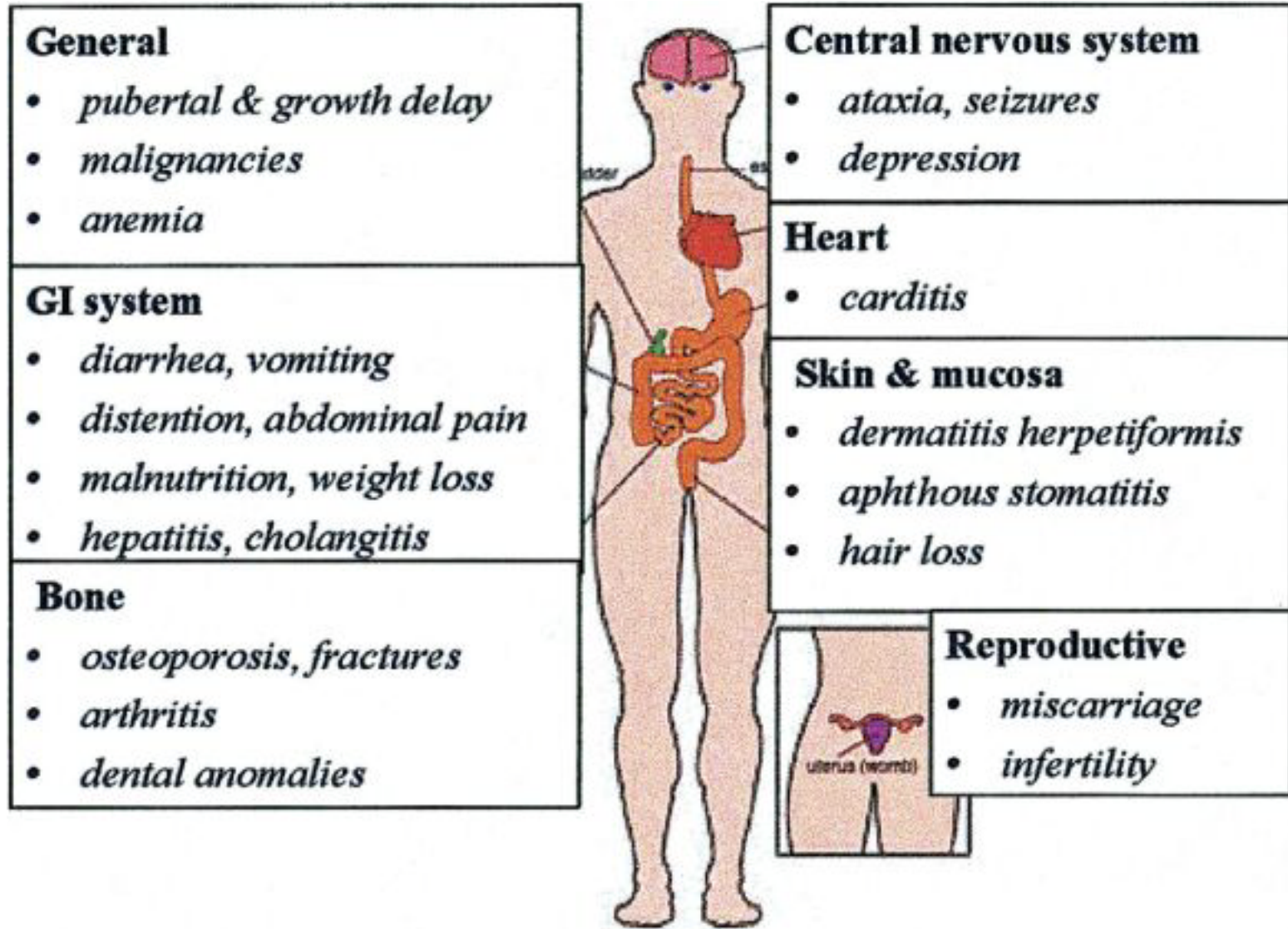
Top 10 *Initial* Diagnoses Given To 600 CD Patients:1996 Survey

- 1. Anemia
- 2. IBS (36%)
- 3. Psychological stress, nerves, imagination
- 4. Diarrhea
- 5. IBD
- 6. Diabetes
- 7. Spastic Colon
- 8. Ulcers
- 9. Virus (Viral Gastroenteritis)
- 10. Chronic Fatigue Syndrome

Iron Deficiency and Occult CD

- 483 hospital lab samples with anemia
 - Men <13.5 gm, Women <11.0 gm
- IgA AEA positive in 32 (6.6%)
 - 28 women (26 pre-menopausal) and 4 men
 - Duodenal biopsy in 25/32
 - 22/25 biopsies consistent with CD
- None of previously diagnosed with CD
- Conclusion: Celiac disease in menstruating women is under-investigated as a potential cause of iron-deficiency anemia

Celiac Disease is also a Systemic Autoimmune Disease



Extraintestinal Manifestations

- Migraines:

- 90 patients with idiopathic migraines tested for celiac disease vs 236 migraine-free controls
- 4% positive vs 0.4% of controls
- Migraines and PET scans improved on gluten-free diet for 6 months

Am J Gastro 2003;98:625-9

- 36 adult CD and 144 healthy controls
 - Major Depressive Disorder 19.4% vs 6.2% ($p<0.05$)
 - Panic Disorder 13.9% vs 2.1% ($p<0.05$)
 - The majority of patients with MDD and PD had antithyroid antibodies ($p<.01$)

J Psychosom Res 2003; 55:573

Extraintestinal Manifestations

- Hyposplenism
- Arthralgia
- Recurrent aphthous stomatitis
- Alopecia
- Peripheral Neuropathy
- Dental enamel hypoplasia
- Infertility
- Delayed puberty
- Osteopenia

Autoimmune Associations

- **IDDM** : 3-8% of childhood diabetics positive for CD
- **Dermatitis herpetiformis** (3.5% of CD)
- **Autoimmune Thyroiditis**: 3.8%
 - Thyroid specific antibodies 14%
- **Alopecia** 1.3%
- **Psoriasis**
- **Rheumatoid arthritis**
- **Abnormal LFTS**
 - Autoimmune hepatitis (4% positive for CD)
 - PBC (6% PBC with CD)
 - Primary sclerosing cholangitis (1-3%)

Studies of the Prevalence of Elevated LFTs in Patients with Celiac Disease

	Number of Patients	% Elevated LFTs	Normal LFT with Gluten-Free Diet
Hagender et al	75	39%	n/a
Bonamico et al	65	60%	n/a
Jacobson et al	132	47%	75%
Bardella et al	158	42%	95%
Novacek et al	178	40%	96%

Studies of the Prevalence of Celiac Disease in Patients with Unexplained LFT Elevations

	Number of Patients	Test Used	Prevalence of Positive Celiac Test(s)	GI symptoms	Small Bowel Biopsy	Normal LFT with Gluten-Free Diet
Volta et al	55	AEA and AGA	9%	none	all	All
Lindgren et al	327	AGA	6%	2/327	50%	70%
Bardella et al	140	AEA and AGA	9%	5/140	12/13	12/13

Irritable Bowel Syndrome and CD

- **Am J. Gastro 2002**: 150 biopsy-proven celiac
 - 30/150 (20%) patients met the ROME criteria for IBS
- **Lancet 2001**: 300 patients in UK with IBS
 - 66 (22%) EMA, AGA positive
 - 14 (4.7%) biopsy-proven celiac
 - Not tested for response to GFD
- **APT 2003**: 105 Iranian patients with diagnosis of IBS
 - 12/105 (11.5%) positive for celiac disease
 - 11/12 had significant improvement on a GFD

Rare Complications of Celiac Disease

- Refractory sprue
- Ulcerative jejuno-ileitis
- Collagenous sprue
- Adenocarcinoma of the small bowel
- Malignant lymphomas
 - Non-Hodgkin Lymphoma O.R. 3.1
 - 1/1421 patient years
 - Intestinal T-cell Lymphomas O.R 40
 - 1/5684 patient years

“To know syphilis is to
know medicine”.

Sir Wm. Osler, M.D (1849 – 1919)

“To know celiac disease
is to know... syphilis”

Sir Thomas Hargrave MD

How is Celiac Disease Diagnosed?

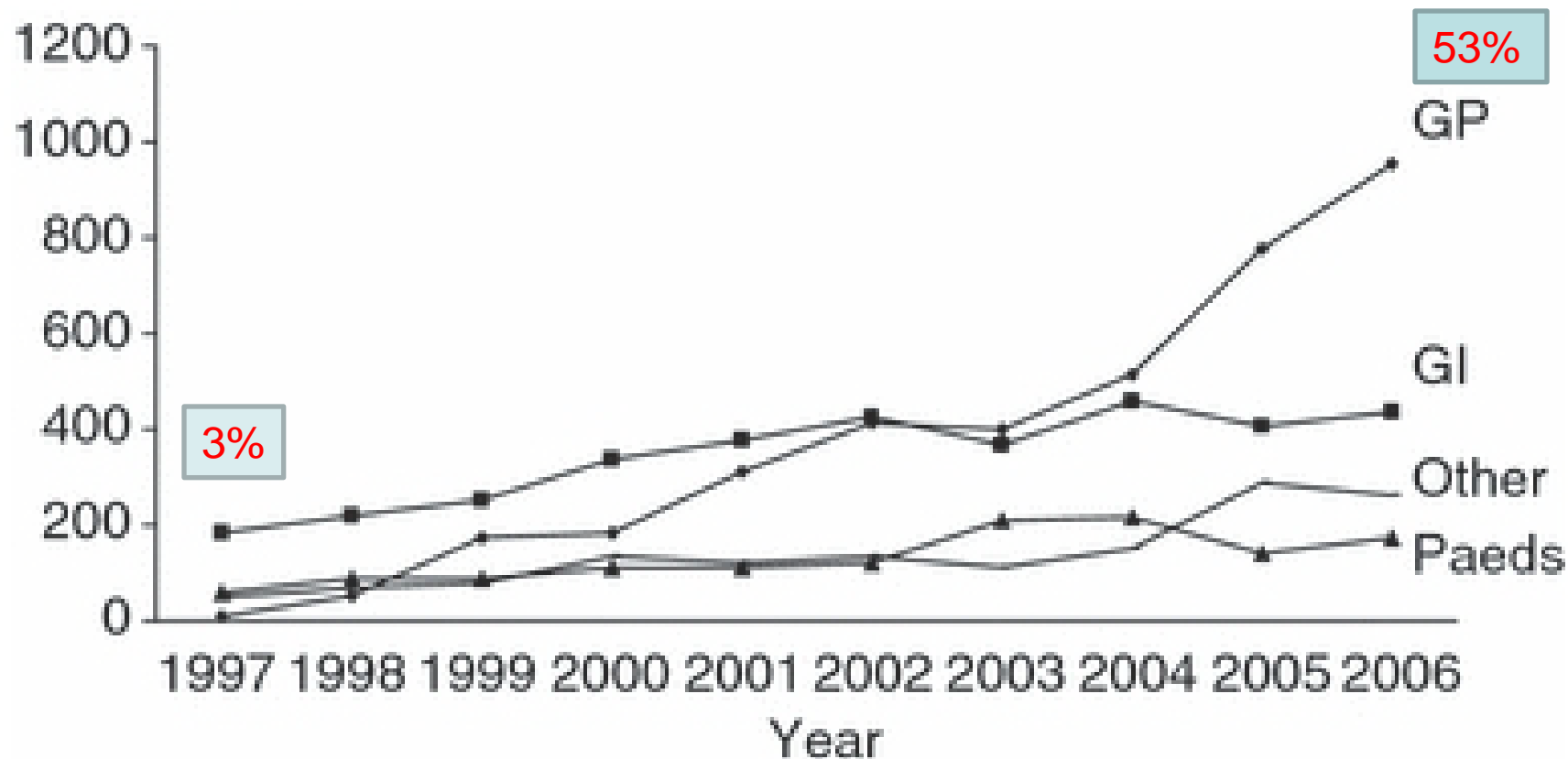
Who is at Risk for CD?

- **1st and 2nd degree relatives 10-15%**
- **Down's Syndrome 12%**
- **Type 1 DM 3-8%**
- **Autoimmune Thyroiditis 5%**
- **Asymptomatic Iron Deficiency 3-6%**
- **Symptomatic (GI) Iron Deficiency 10-15%**
- **Microscopic Colitis 15-21%**
- **IBS 3-4%**
- **Chronic Fatigue Syndrome 2% ???**

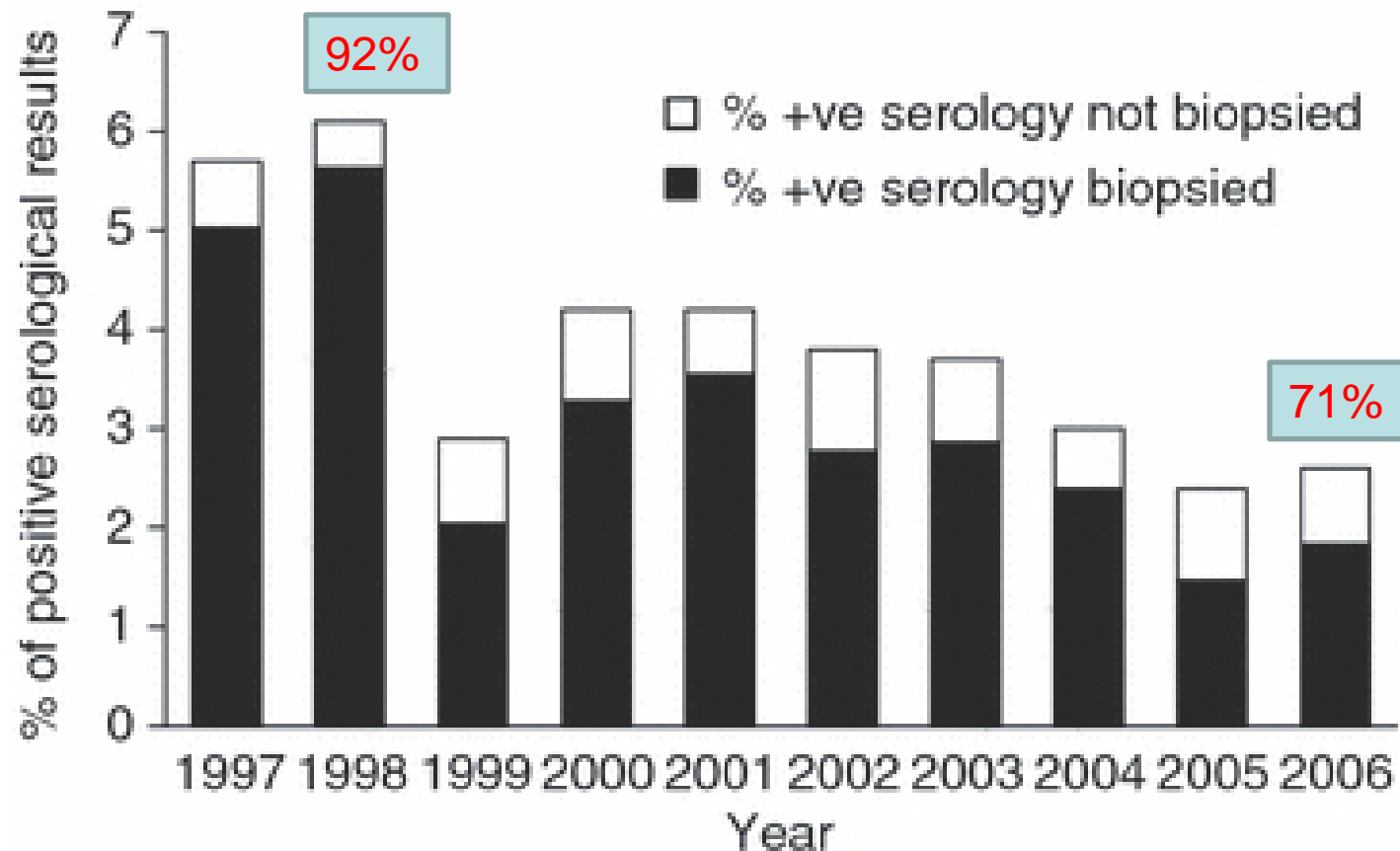
Diagnosis of Celiac Disease

- No one test can definitively diagnose or exclude celiac disease in every individual
 - Tests must be performed while the patient is on a gluten-containing diet
- The best available tests are:
 - **IgA endomycial antibody immunofluorescence (EMA)**
 - **IgA anti-human tissue transglutimase (tTG)**
- A positive EMA test is virtually 100% specific for CD, pooled sensitivity 95-97%
- Total IgA should be checked, since selective IgA deficiency is 10-15 times more common in CD than the general population

Changing Pattern of Celiac Disease Serology Requests



Changing Pattern of Celiac Disease Serology Requests



Antigliadin Antibodies Have a Relatively Low Sensitivity and Specificity: Do Not Order

TABLE 2. SENSITIVITY AND SPECIFICITY AND POSITIVE AND NEGATIVE PREDICTIVE VALUES OF SEROLOGIC TESTS FOR UNTREATED CELIAC SPRUE.

SEROLOGIC TEST	SENSITIVITY*	SPECIFICITY*	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
	percent			
Test for IgA antiendomysial antibody				
Indirect immunofluorescence assay	85–98	97–100	98–100	80–95
ELISA that uses guinea pig tissue transglutaminase†	95–98	94–95	91–95	96–98
Dot blot test that uses human tissue transglutaminase	93	99	99	93
Test for IgA antigliadin antibodies	75–90	82–95	28–100	65–100
Test for IgG antigliadin antibodies	69–85	73–90	20–95	41–88

*There are wide variations in the sensitivity and specificity of these tests among different laboratories. The data on tissue transglutaminase antibodies are based on three recent large studies.^{31–33}

†ELISA denotes enzyme-linked immunosorbent assay.

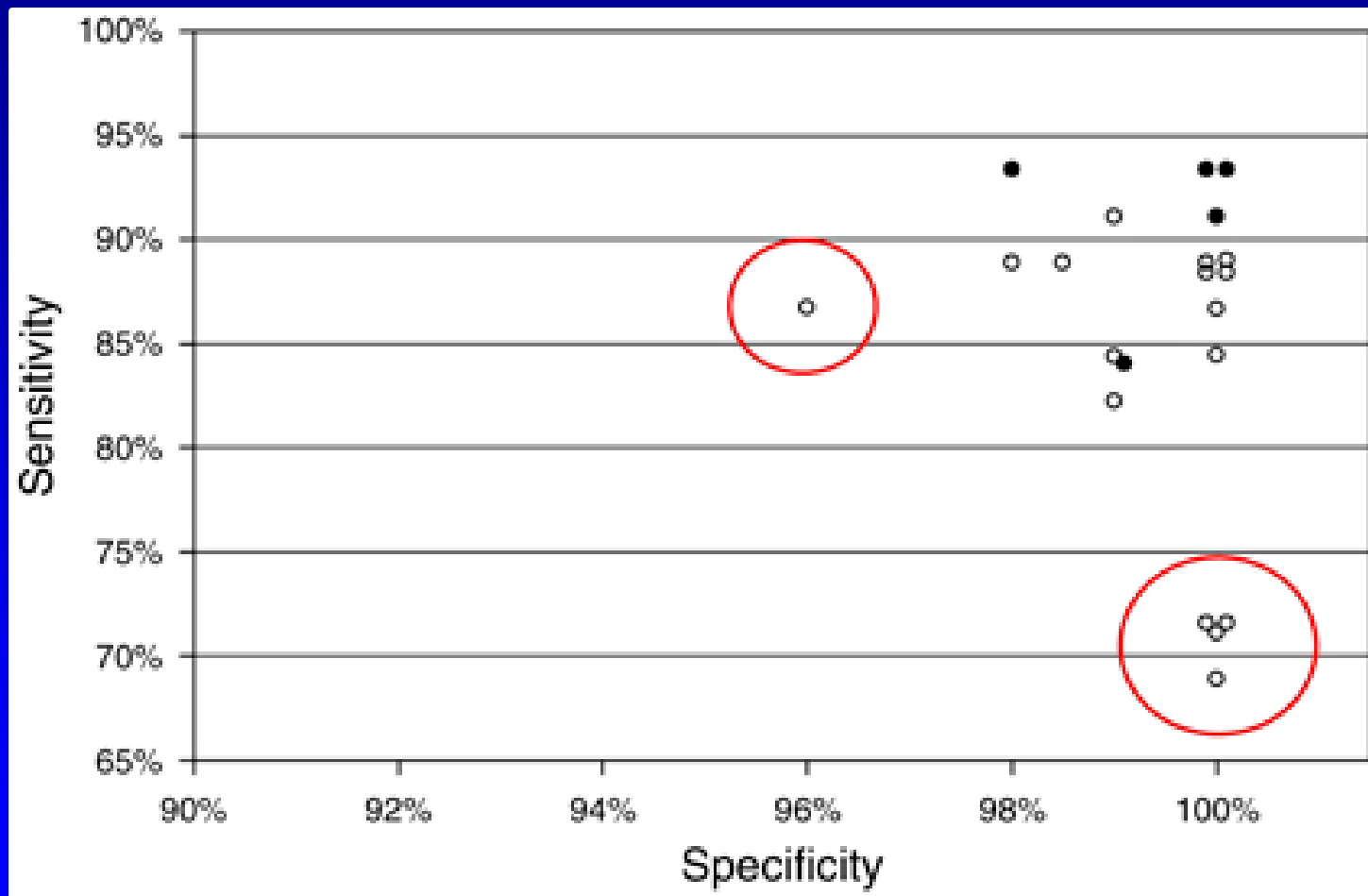
Tissue Transglutimase Antibodies

- Both tTG antibody assays, against guinea pig (tTG-GP) and human recombinant antigens (tTG-HR), have high reported sensitivity and specificity
- Pooled sensitivity of tTG-GP 90% and TTG-HR 98%
- Pooled specificity of tTG-GP 95% and TTG-HR 99%
- TTG can be falsely positive in presence of cirrhosis, diabetes, severe CHF and various auto-immune disorders

Variable Sensitivity of Transglutaminase Autoantibodies (TGAA)

- **International Transglutaminase Autoantibody Workshop for Celiac Disease**
- **A total of 20 laboratories (5 commercial laboratories, 15 research and clinical laboratories) participated that included enzyme-linked immunosorbent assay (ELISA) and radiobinding assays.**
- **A total of 150 serum samples were distributed to each laboratory, with each laboratory receiving an equal aliquot that was coded and blinded, composed of 100 healthy control sera and 50 CD sera.**
- **Laboratory sensitivity ranged from 69% to 93% and specificity ranged from 96% to 100%**

Variable Sensitivity of Transglutaminase Autoantibodies (TGAA)



Mild Disease = Lower Sensitivity

- The majority of published studies on sensitivity and specificity of tTG and EMA used populations with a CD prevalence of 30-45%
- The positive predictive value of the TTG and EMA drop significantly if tested against a population prevalence of 1%
- The sensitivity of both tTG and EMA also appear to depend on the severity of mucosal injury (Marsh classification)

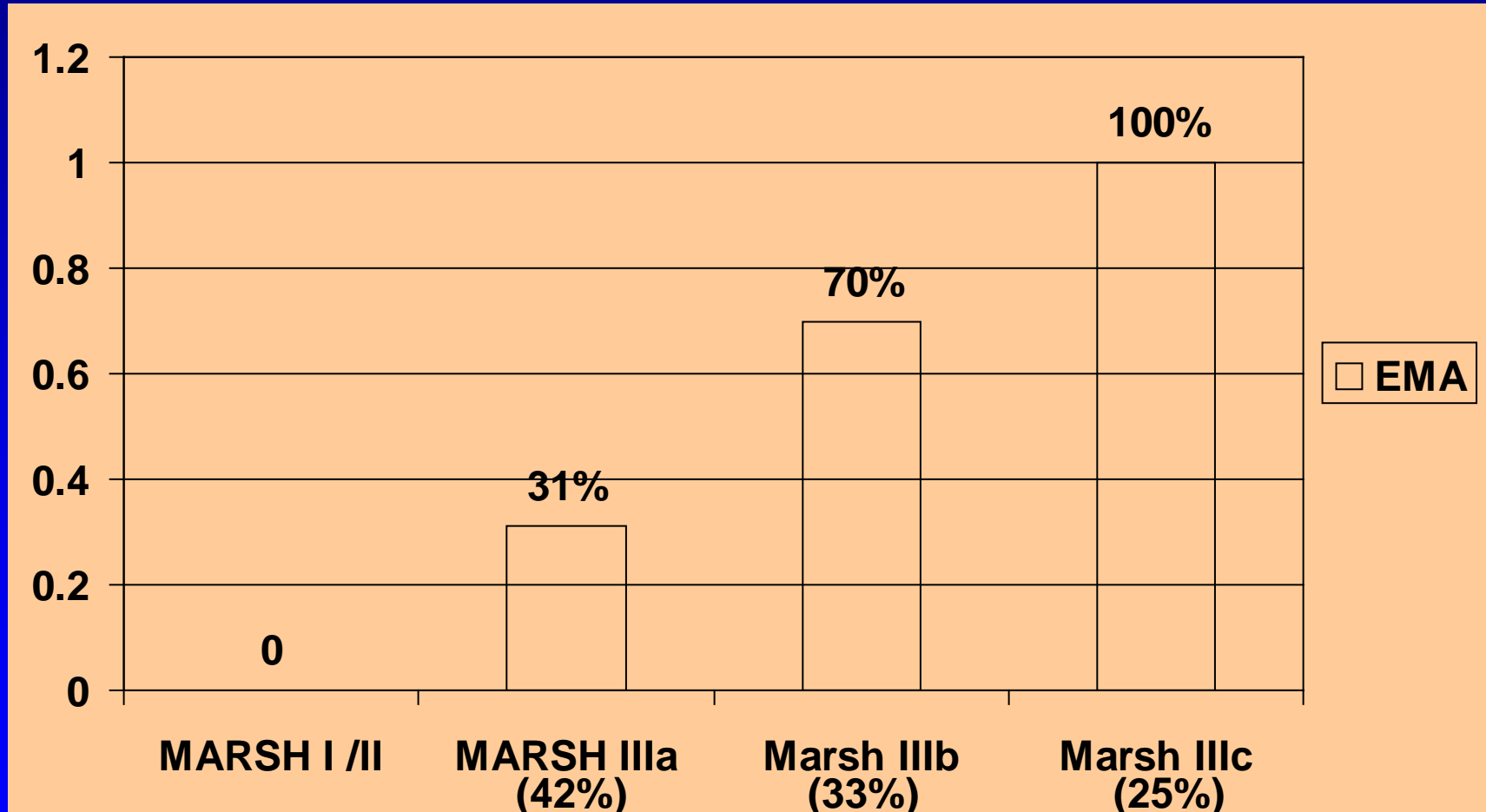
Low Sensitivity of tTG Assay

- **Plenary at 2004 ACG: 117 biopsy-confirmed celiac cases**
 - **Serum for tTG IgA assay sent to 4 community commercial laboratories**
 - **Overall sensitivity only 71%/ specificity 67%**
 - **Total villous atrophy (Marsh IIIc) 92%**
 - **Partial villous atrophy (Marsh IIIa) 38%**

Low Sensitivity of AEA in Mild CD

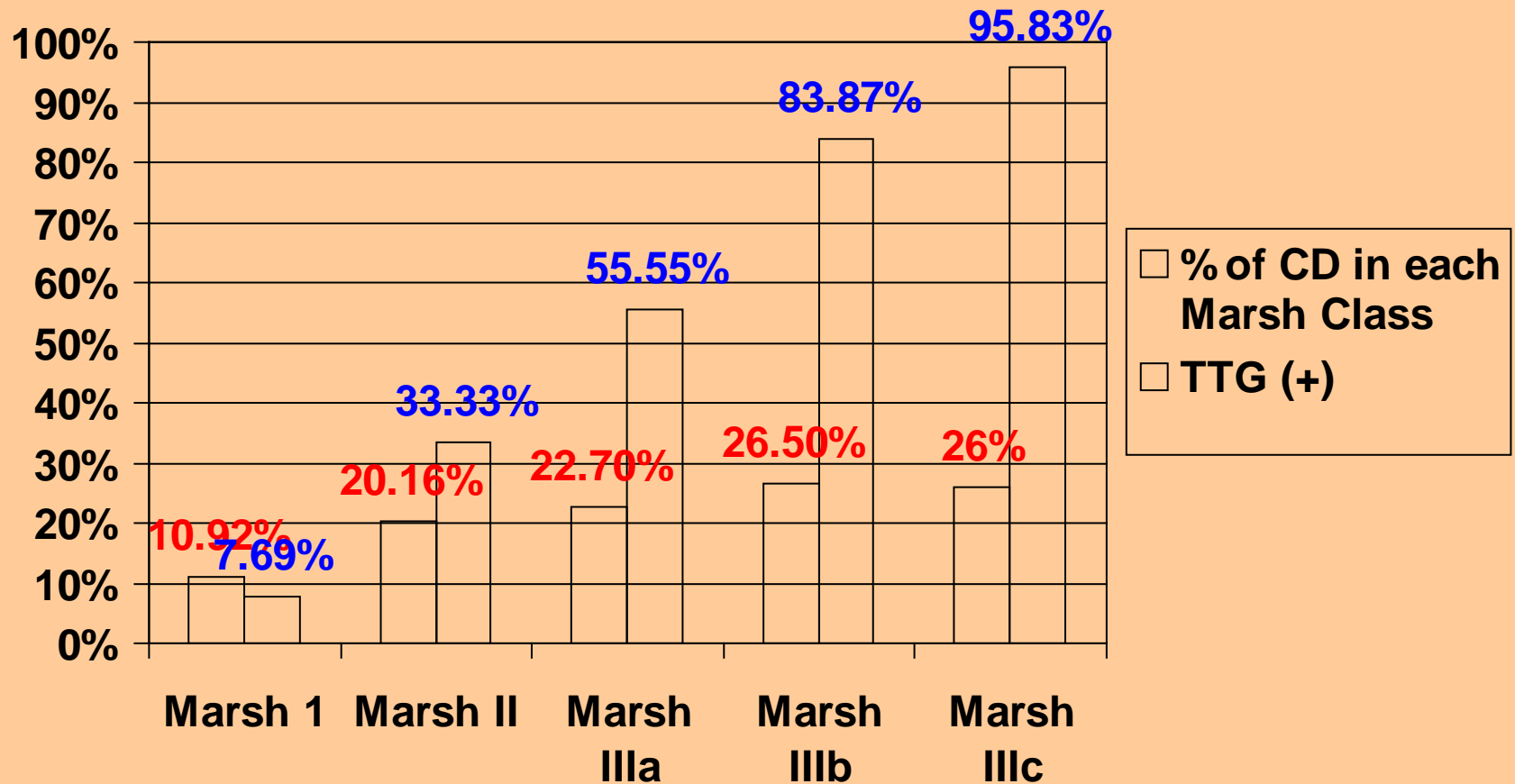
- In a study of patients with established CD, and their first degree relatives, none of the patients with the mildest forms (Marsh I and II) had a positive AEA.
 - **Total villous atrophy (Marsh IIIc) 100%**
 - **Partial villous atrophy (Marsh IIIa) 31%**
- (Am J. Gastro 1999; 94:888)**

Sensitivity of EMA in 69 CD and 16 First-Degree Relatives



(Am J. Gastro 1999; 94:888)

Sensitivity of tTG Based on Marsh Lesions in 119 Consecutive Adult Celiacs

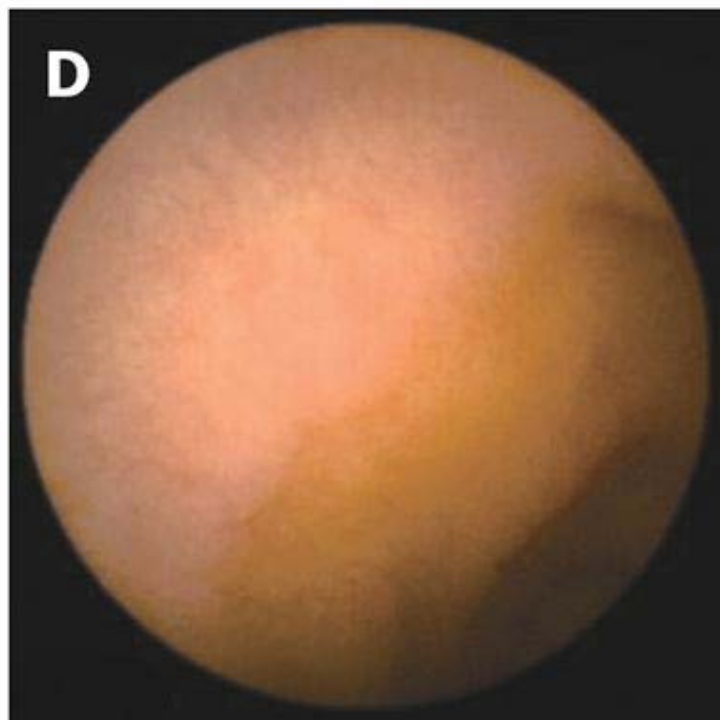
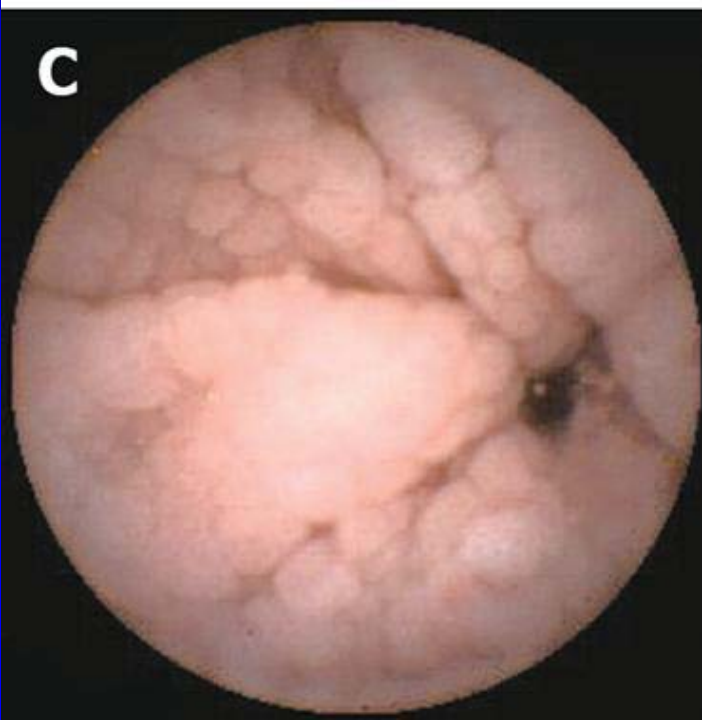
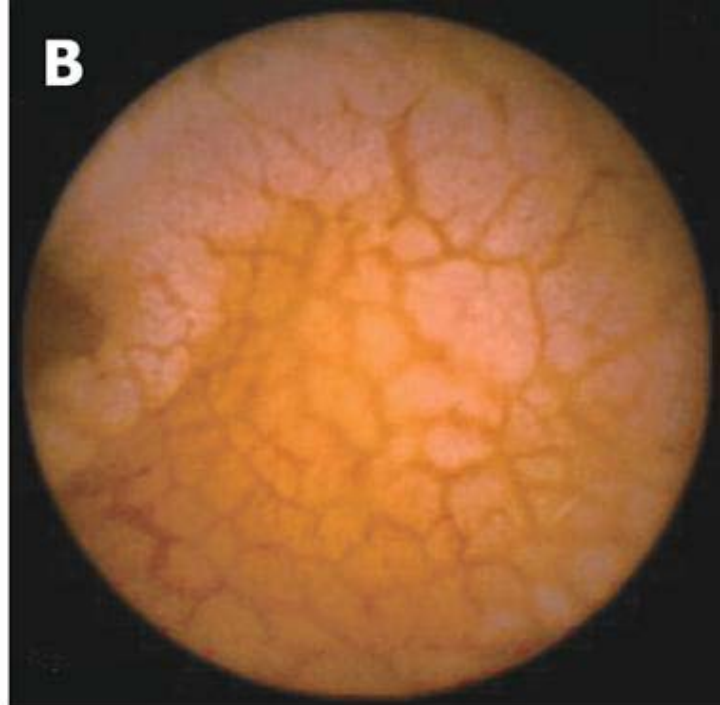
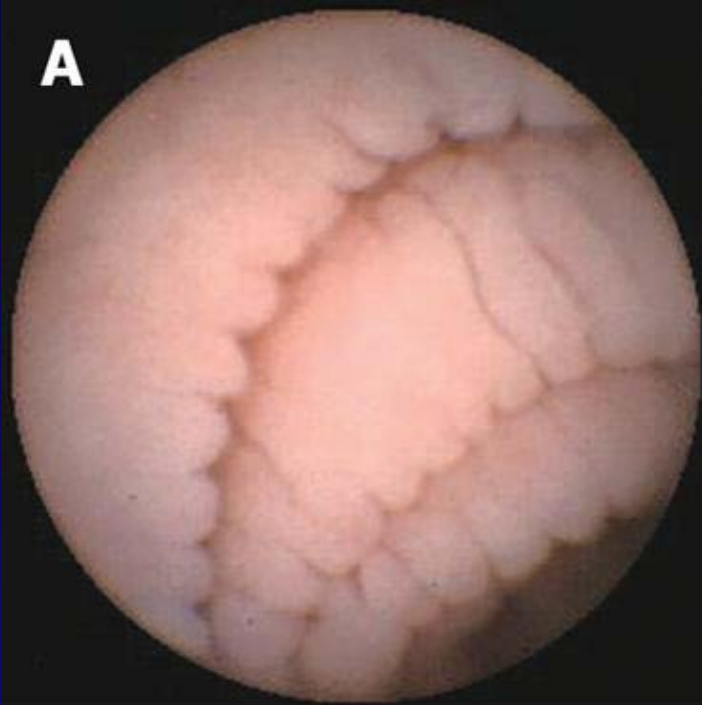


CD Serology: Summary

- The diagnostic accuracy of tTG, and EMA are greatest (>90%) for the more severe forms of celiac disease (total and subtotal villous atrophy)
- The false negative rate may be as high as 65-70% for partial villous atrophy which may account for >40% of CD
- Antibody-negative celiac disease is reportedly associated with the same spectrum of clinical symptoms as antibody-positive CD
- Consider IgA deficiency
- If a definitive diagnosis is needed, small bowel biopsy remains the gold standard

CD Diagnosis: Biopsy

- Although tTG and EMA have very high specificity, duodenal biopsies should be taken in all patients with positive CD serology
 - Latent CD will have a normal /near-normal bx
- Negative celiac serology does not rule out the possibility of CD, especially Marsh IIIa or milder disease
- If serology negative, consider duodenal biopsy in patients with iron deficiency, folate deficiency, malabsorption, unexplained weight-loss, idiopathic elevation of LFTs, refractory “functional” symptoms



Response to Gluten-Free Diet Does NOT Make the DX of CD

- **Placebo response to GFD in IBS as high as 70%**
- **Gluten (increased prolamines) is difficult to digest**
- **GFD often eliminates other dietary factors which may exacerbate IBS symptoms**
- **GFD of associated with elimination of many high-calorie processed and fast foods**

Treatment

Principles of Treatment

- **Life-long adherence to a gluten-free diet**
Consultation with a skilled dietician
- **Education about the disease**
- **Identification and treatment of nutritional deficiencies**
 - **Iron deficiency**
 - **Prevention of bone loss**
- **Access to an advocacy group (Celiac.com)**

Life-long Gluten-Free Diet

- A gluten-free diet is the only proven therapy for CD
- Approximately 70% of patients have symptomatic improvement within 2 weeks of a GFD
- It is not clearly established how strict the GFD has to be for any given patient to avoid symptoms or complications
- Dietary/nutrition counseling is essential
- Histologic improvement lags clinical response and can take of to 18 months to normalize

**TABLE 3. DIETARY GUIDELINES FOR PATIENTS
WITH CELIAC SPRUE.***

Avoid all foods containing wheat, rye, and barley gluten.

Avoid all foods containing oats (at least initially).

Avoid foods containing lactose initially.

Use only rice, corn, maize, buckwheat, potato, soybean, or tapioca flours, meals, or starches.

Look for foods that have the gluten-free symbol.

Try foods containing wheat starch from which gluten has been removed after the diagnosis of celiac sprue is established.

Read all labels and study the ingredients of processed foods.

Beware of gluten in medications, food additives, emulsifiers, and stabilizers.

Avoid all beers, lagers, ales, and stouts.

Wine, liqueurs, most ciders, and other spirits, including whiskey and brandy, are allowed.

Give essential medications parenterally initially if malabsorption is severe.

*Modified from Trier⁵¹ with the permission of the publisher.

Treatment: Life-long Gluten-Free Diet

- Total avoidance of gluten is extremely difficult
- Considerable controversy exists over what constitutes a gluten-free diet or gluten-free products
- Wide individual variability in gluten sensitivity
- The exact amount of gluten that CD patients can tolerate without deleterious effects has not been established
- 2008 FDA guidelines: Gluten-Free = < 20 ppm or less than 6 mg

Gluten-Free Diets Are Difficult

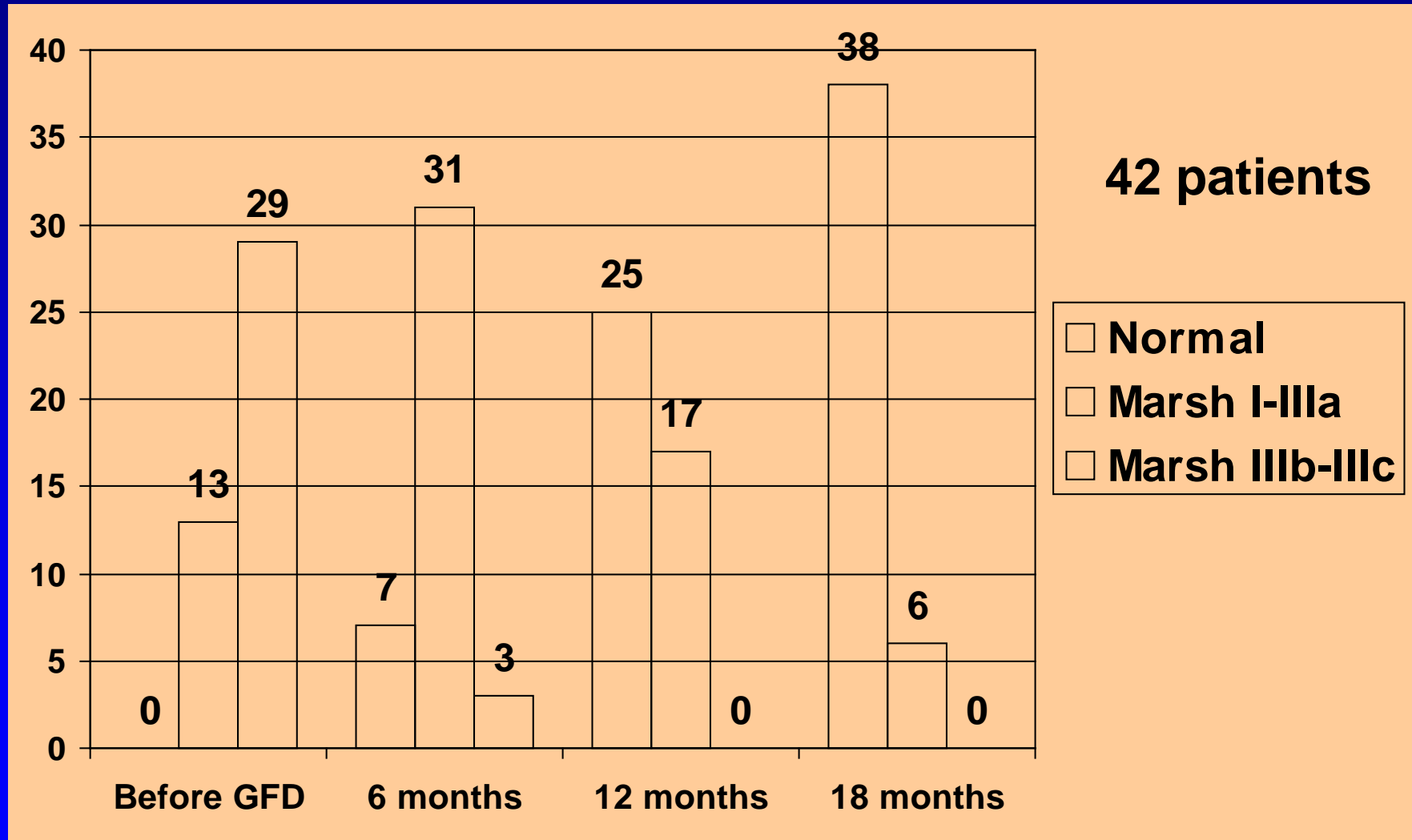
- 44% of adults found a GFD very or moderately difficult to follow
- A survey of 253 CD adult revealed that a GFD negatively impacted ability to eat out (86%), travel (82%), attend family functions (67%), or work/career (41%)
- 21-26% report dietary lapses at social functions and restaurants

Monitoring Treatment Response

- Long-term follow up study of 380 CD patients mean 6.9 +/- 7.5 years
- Repeat biopsy after a minimum of 2 years of a GFD
 - Biopsy normal: 43.6%
 - Partial atrophy :32.6%
 - Total atrophy 23.8%
- Lack of dietary compliance was the best predictor of biopsy results.

Digestion 2002;66(3):178-85

Resolution of CD Histology on GFD



Treatment Outcomes

- 381 adult patients with biopsy-proven celiac disease followed at Mayo Clinic
- 241 (175 women) had both a diagnostic and follow-up biopsy available for re-review.
- 34% of patients complete mucosal recovery at 2 years following diagnosis
- 66% of patients complete mucosal recovery at 5 years (95% CI: 58–74 %)

Treatment Outcomes

- 82% of patients showed some clinical response to the gluten-free diet, but clinical response was not a reliable marker of mucosal recovery ($P = 0.7$).
- The overall rate of good adherence to GFD was 66% (156/241)
- Only 67 (43%) of 156 patients with good adherence to a GFD, as determined by the dietitian interview, achieved mucosal recovery
- Patients who complied poorly with a gluten-free diet ($P < 0.01$), those with severe celiac disease defined by diarrhea and weight loss ($P < 0.001$), and those with total villous atrophy at diagnosis ($P < 0.001$) had high rates of persistent mucosal damage.

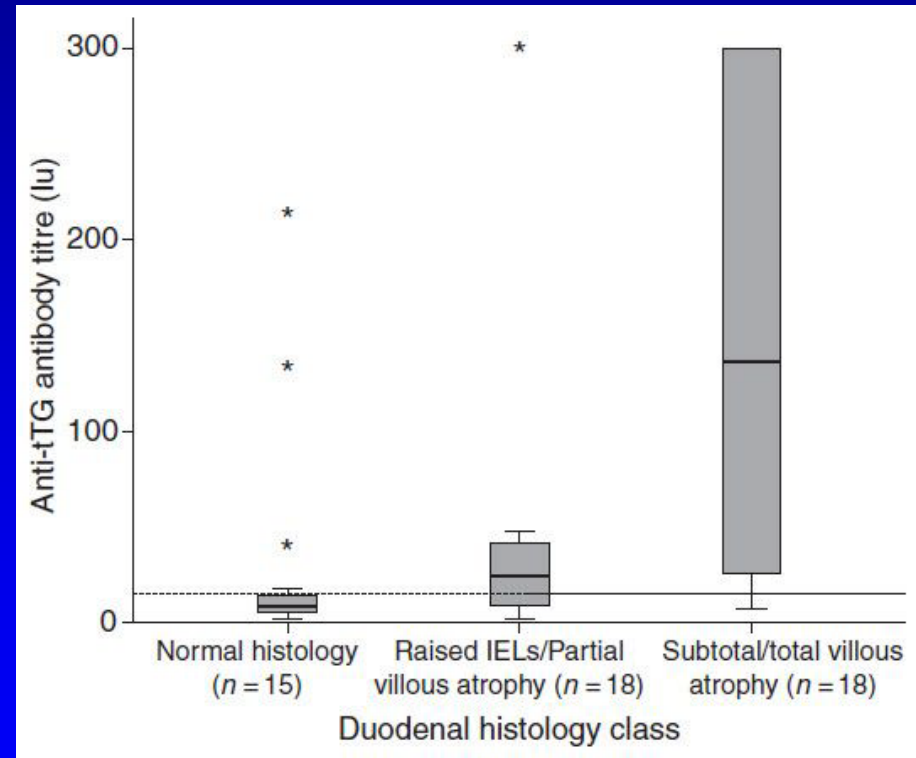
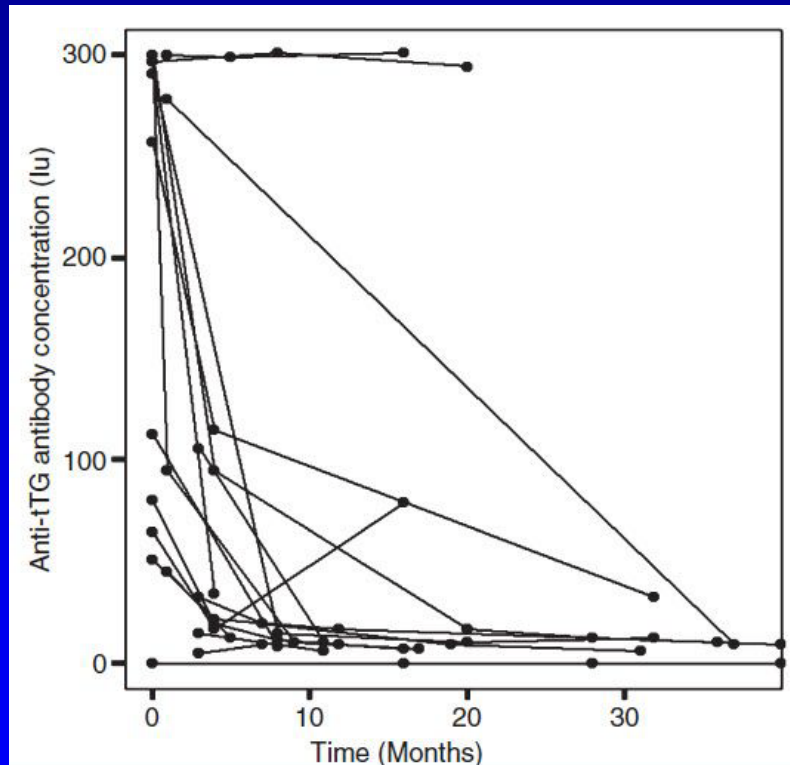
Monitoring Treatment Response

- Repeat duodenal biopsy is useful but not necessary
- Complete mucosal recovery may take 18 months or longer
- Serology is an approximate marker of dietary compliance but may take up to one year to normalize in adults
- Persistently elevated serology suggests lack of compliance or unintended gluten ingestion
- No established protocol exists for screening for small bowel adenocarcinoma or lymphoma

Anti-tTG Antibodies in the Follow-up of Adult Celiac Disease

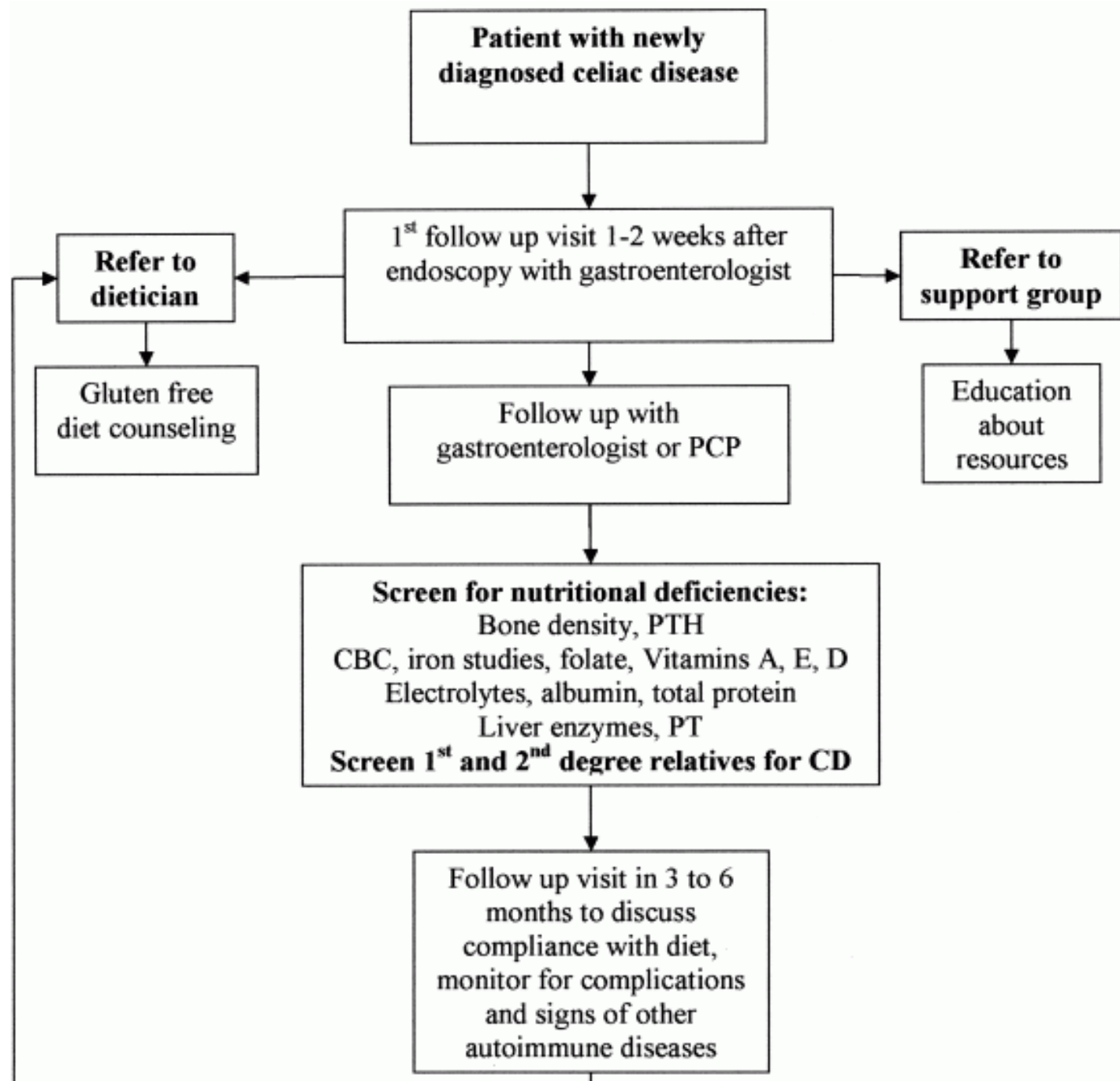
- 54-month cohort follow-up study, 182 adult patients were assessed.
- Data recorded included self-assessment of GFD adherence; anti-tTG antibody concentration and duodenal biopsy
- Anti-tTG antibody concentrations fell rapidly following successful initiation of a GFD, and maintenance of normalization identified those who continued to be adherent to the diet.
- Persistently elevated anti-tTG antibody levels were significantly associated with abnormal duodenal histology ($P < 0.001$), low ferritin ($P < 0.01$) and poor adherence to the GFD ($P < 0.001$).

Anti-tTG Antibodies in the Follow-up of Adult Celiac Disease



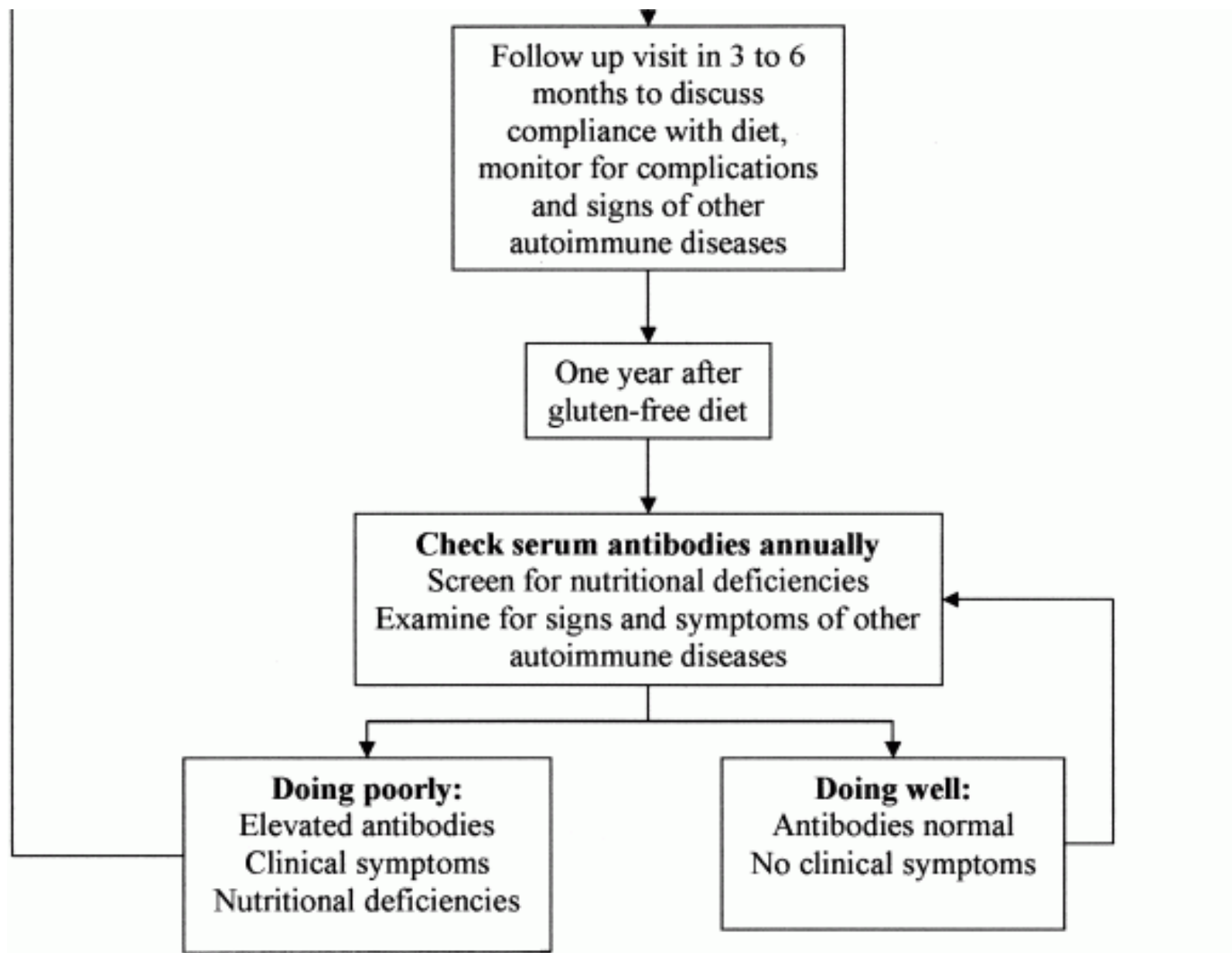
Conclusions

- Celiac disease is a prevalent but vastly under-diagnosed systemic auto-immune disease
- The classic presentation is uncommon in adults, especially in patients over 60
- Serology specificity very high but sensitivities are not as high as generally believed and should not be relied upon to exclude CD
- A high index of suspicion is indicated, especially when patients have unusual functional complaints, or evidence of a predisposition to autoimmune diseases



Treatment: Life-long Gluten-Free Diet

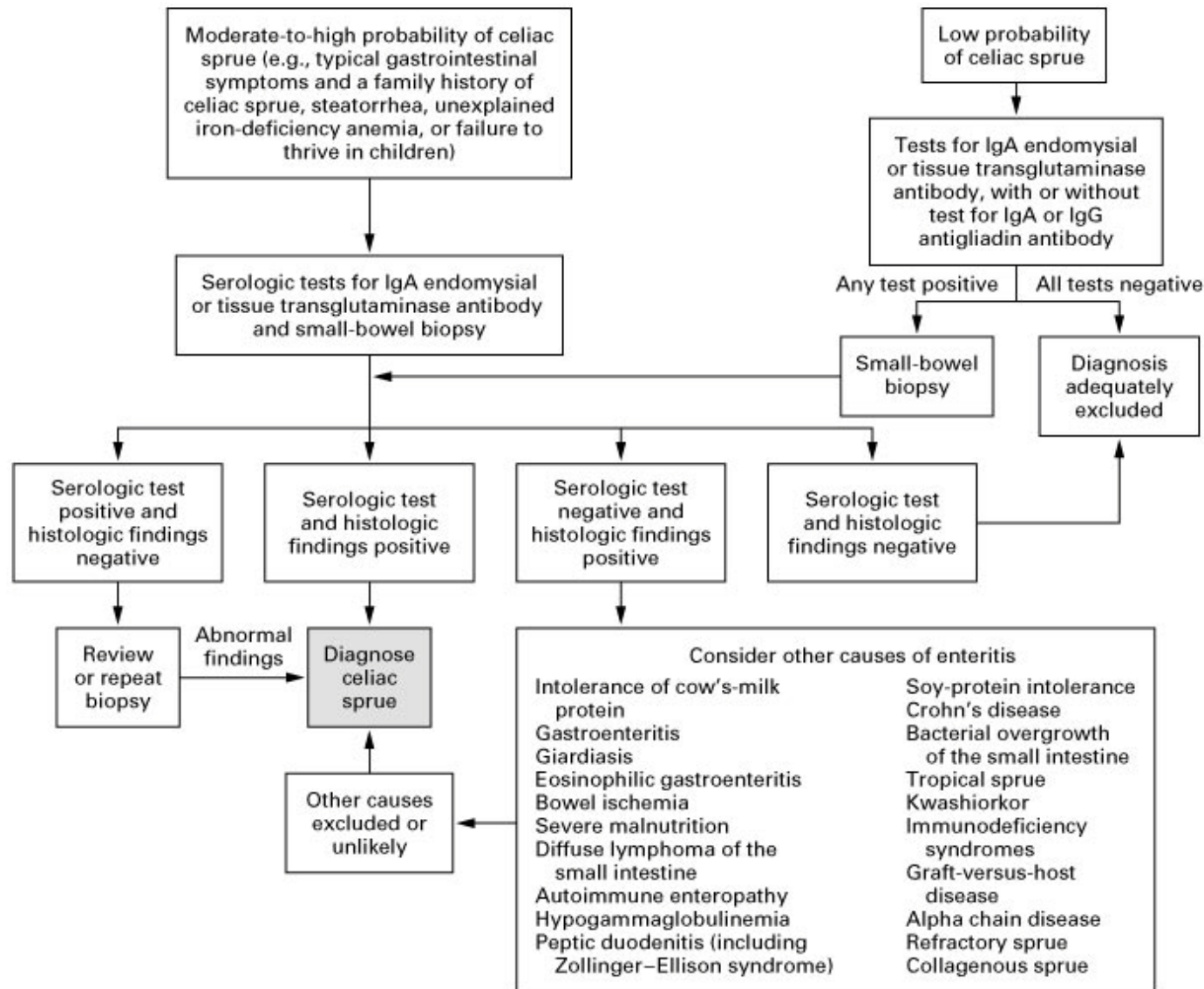
- **Persistent symptoms usually indicate incomplete dietary adherence**
- **Dairy products should be initially avoided since secondary lactase deficiency is common**
- **Complete elimination of gluten is very difficult to obtain**
- **Food labels are often ambiguous**



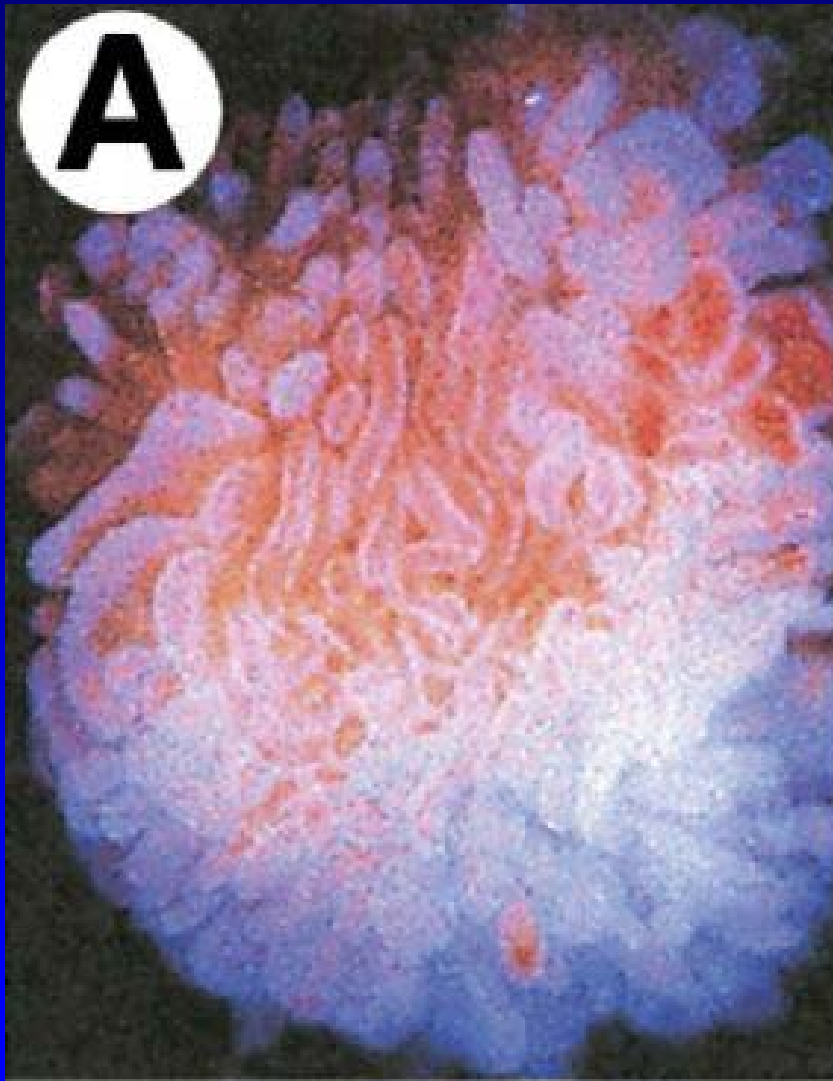
Diagnosis of Celiac Disease: Biopsy

- Endoscopic biopsies from the second duodenum are current gold standard
- Biopsies of the proximal small intestine are indicated in all individuals with a positive celiac antibody test
- Total and subtotal villous atrophy can be visually diagnosed on endoscopy as well
- In adults, tropical sprue, HIV-enteropathy most likely to mimic CD

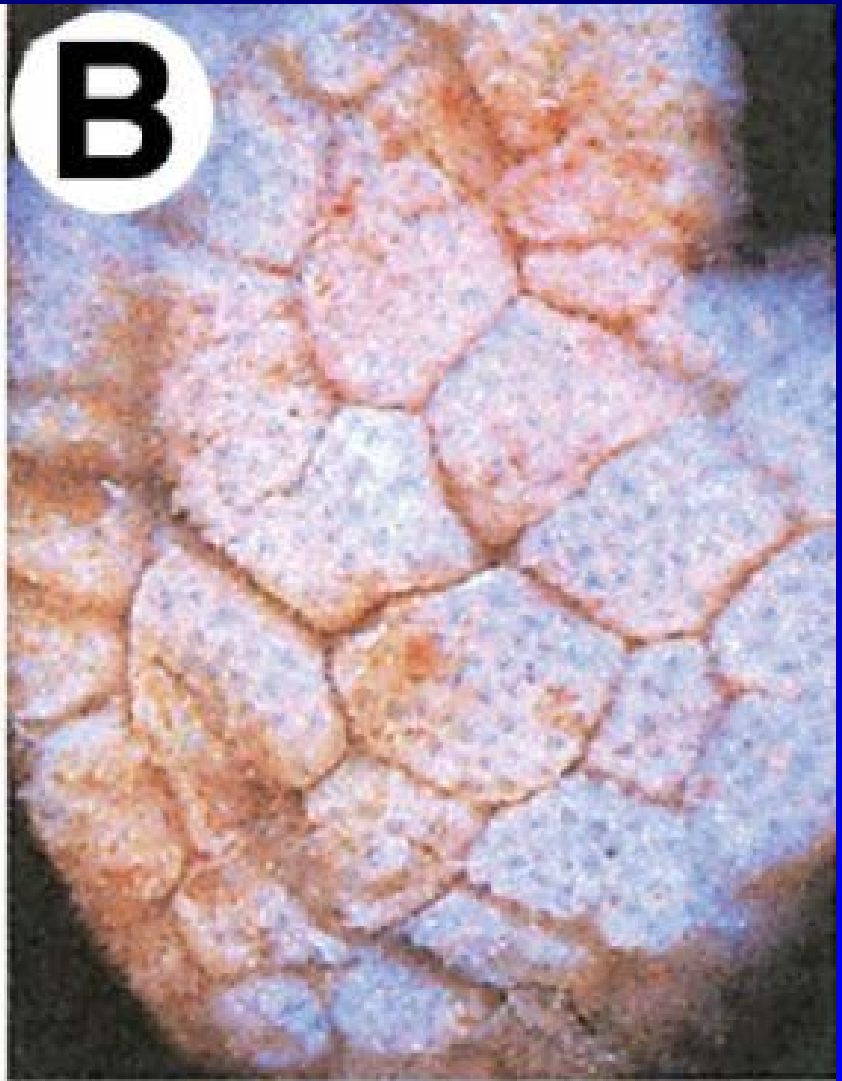
Approach to the Diagnosis of Celiac Sprue



A



B



Pathophysiology

- These changes decrease the amount of epithelial surface available for digestion and absorption in the involved bowel
- Many mucosal enzymes are altered due to the damage to the absorptive cells
- Decrease in disaccharidases, peptidases, alkaline phosphatase, ATPase, and esterases

FEW OR NO SYMPTOMS

SYMPTOMS



**LITTLE
MALABSORPTION**

**MINIMAL
MALABSORPTION**

**EXTENSIVE
MALABSORPTION**

**MINIMAL VILLOUS
ATROPHY
LITTLE CRYPT
HYPERPLASIA**

**PARTIAL VILLOUS
ATROPHY
SOME CRYPT
HYPERPLASIA**

**COMPLETE VILLOUS
ATROPHY
MARKED CRYPT
HYPERPLASIA**

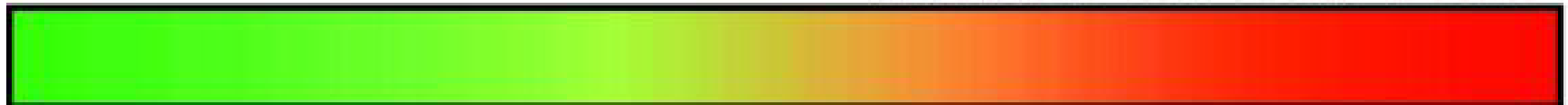
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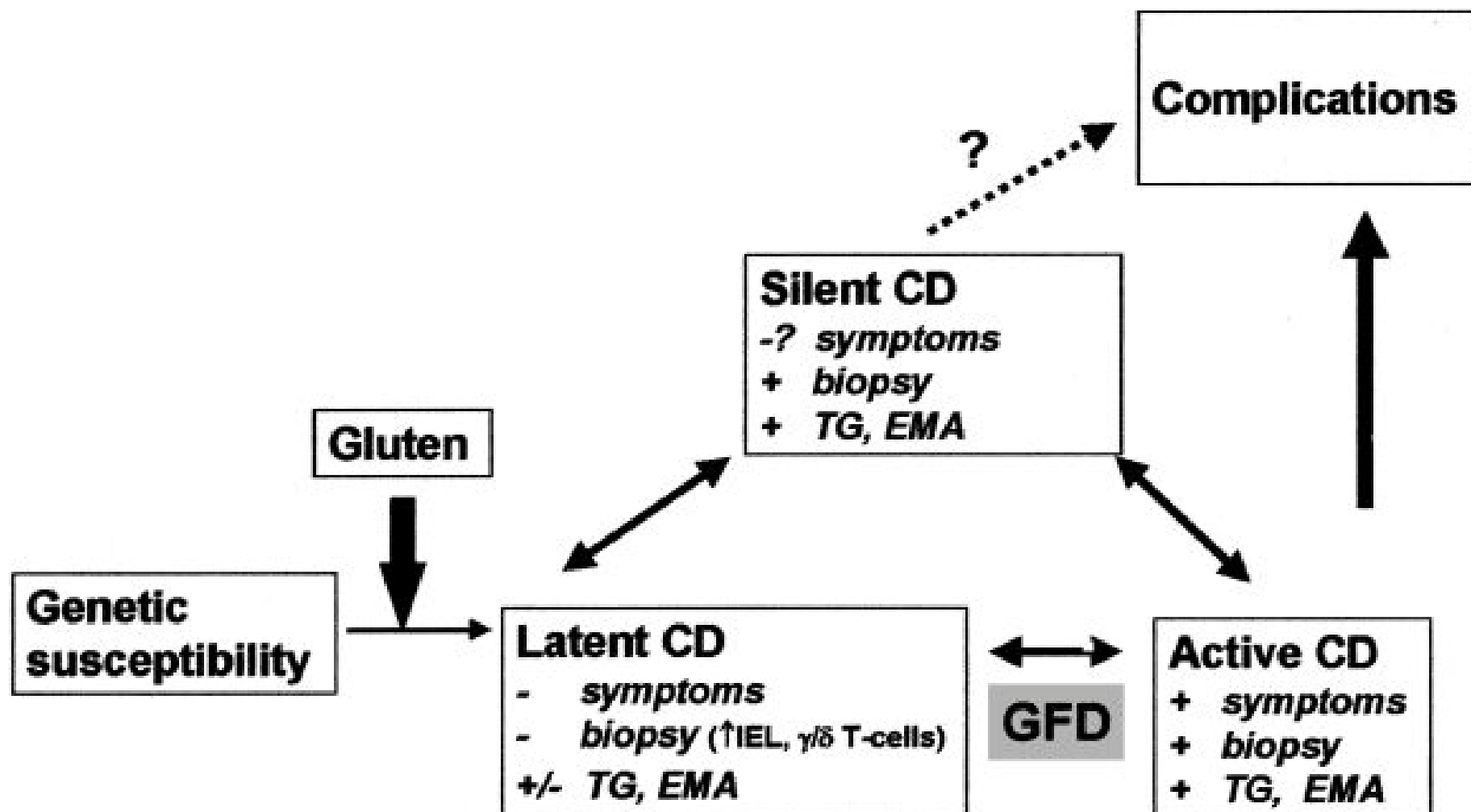
FEW IF ANY G.I. SYMPTOMS

MARKED G.I. SYMPTOMS

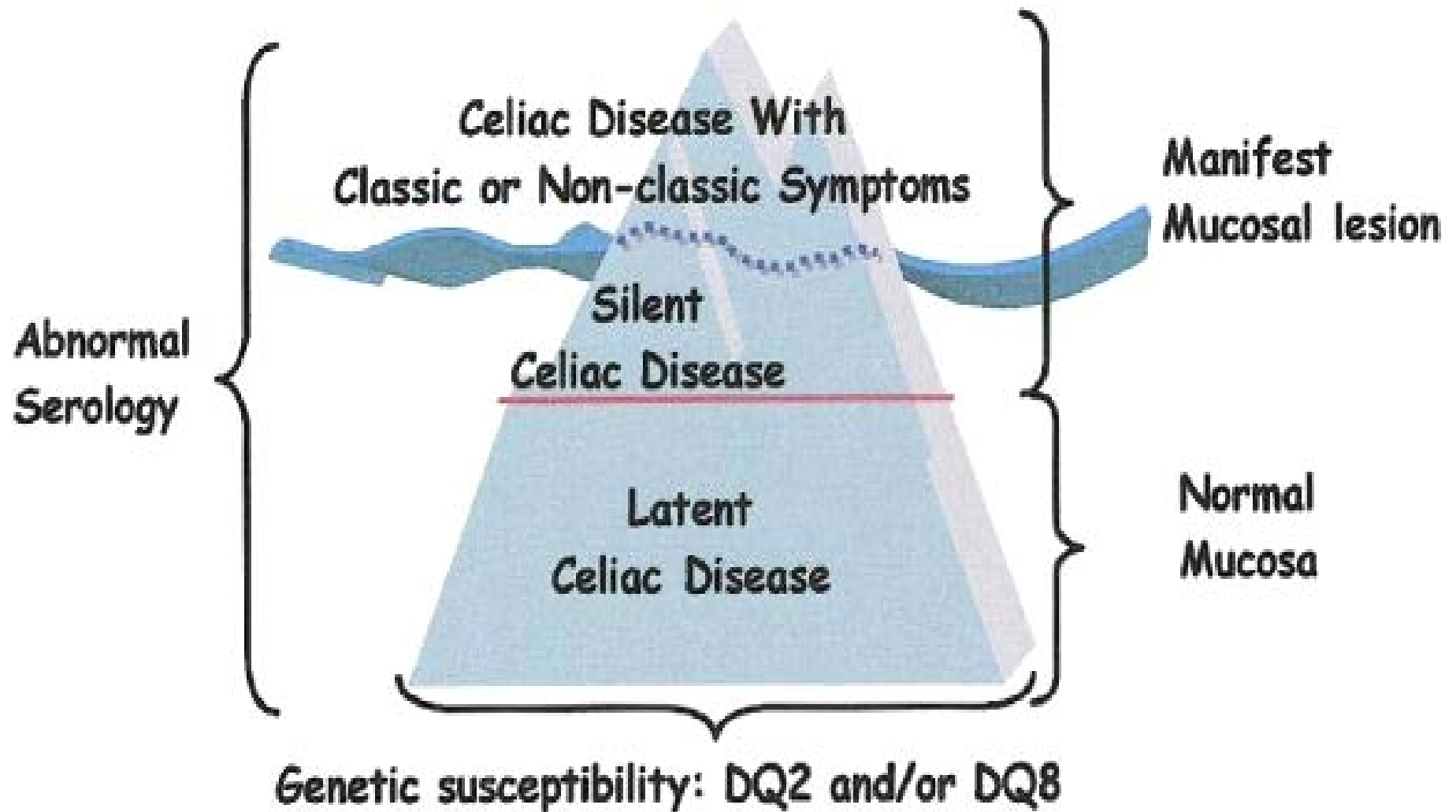


**TIRED, NO ENERGY
IRRITABLE, DEPRESSED
MENSTRUAL DISTURBANCE
WEAKNESS, INFERTILITY
GROWTH DISTURBANCE
NEUROLOGIC COMPLAINTS**

**DIARRHEA
BULKY, PALE, FOUL STOOLS
DISTENTION, LOTS OF GAS
CRAMPS, WEIGHT LOSS
LOSS OF APPETITE OR
VORACIOUS APPETITE**



General Population	1%
Type 1 Diabetes	3-6%
First-degree relatives	20%
Asymptomatic Iron Deficiency	3-6%
Symptomatic Iron Deficiency	10-15%
Osteoporosis	1-3%

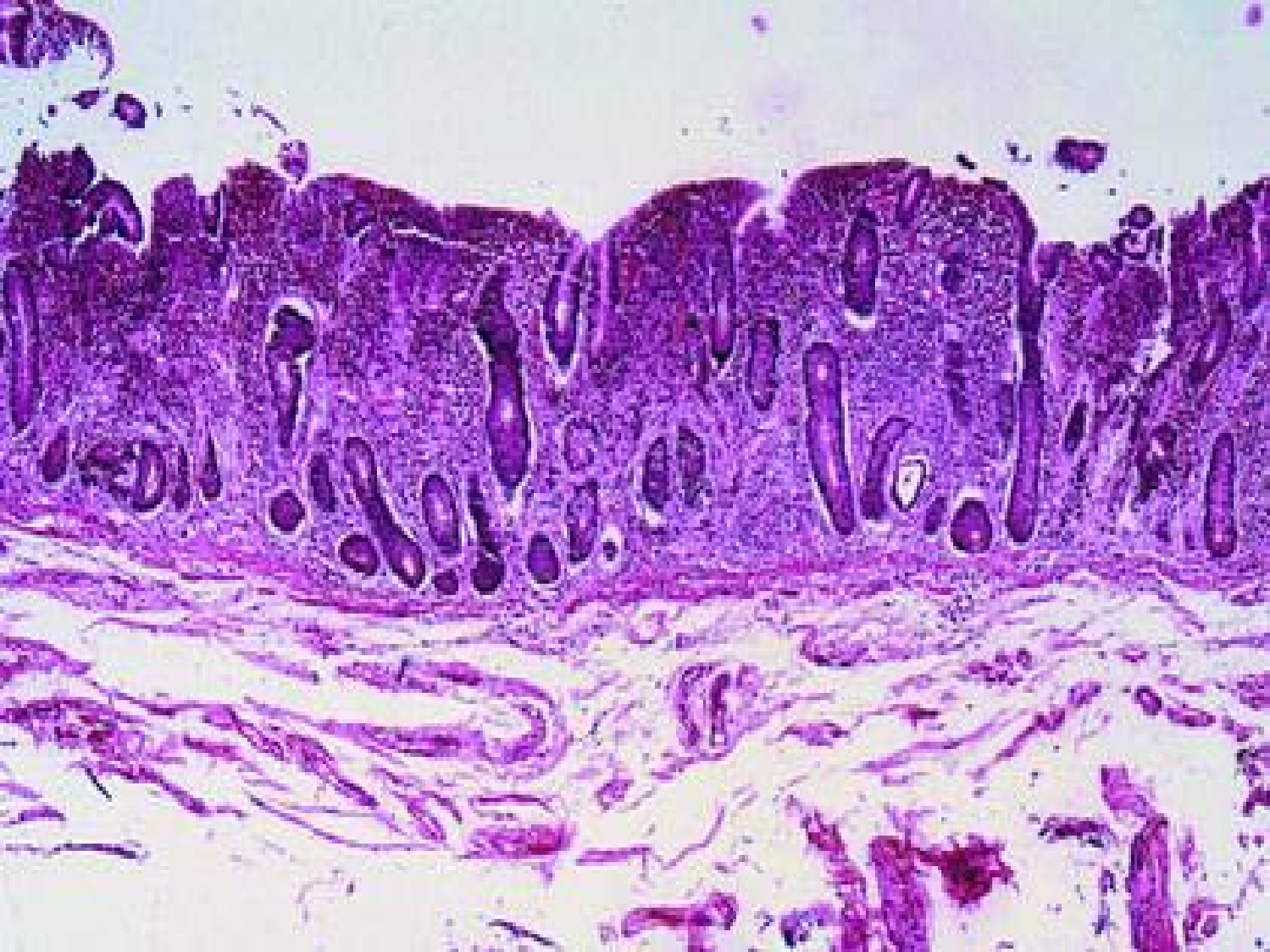




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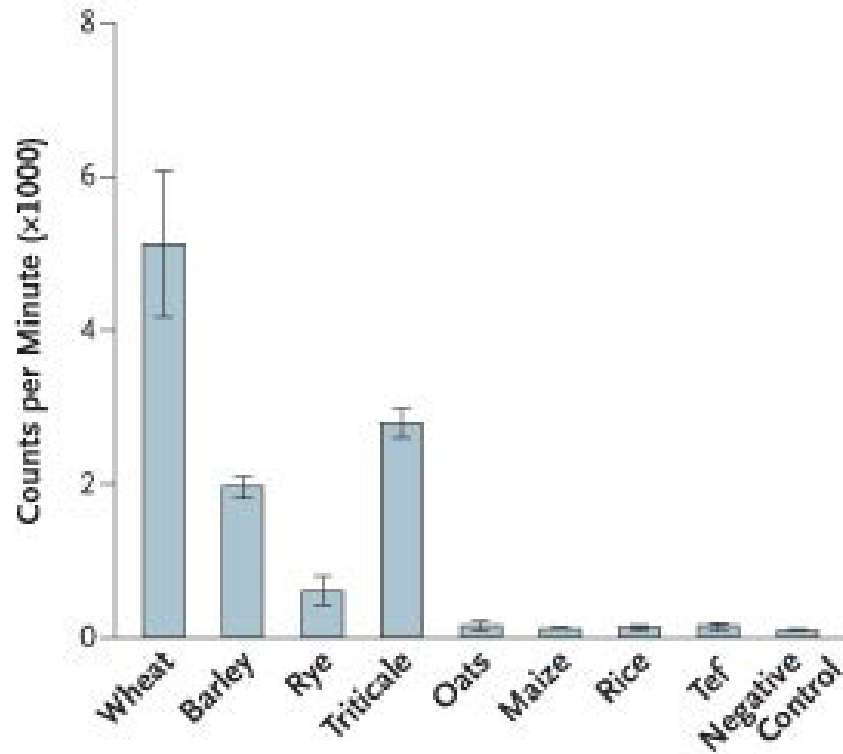
Causes of Small Intestinal Villous Atrophy Other than Celiac Disease

- Bacterial overgrowth
- Crohn's disease
- Cow's milk protein intolerance (children)
- Eosinophilic gastroenteritis
- Giardiasis
- Lymphoma
- Peptic duodenitis
- Post gastroenteritis
- Tropical sprue
- Zollinger-Ellison syndrome

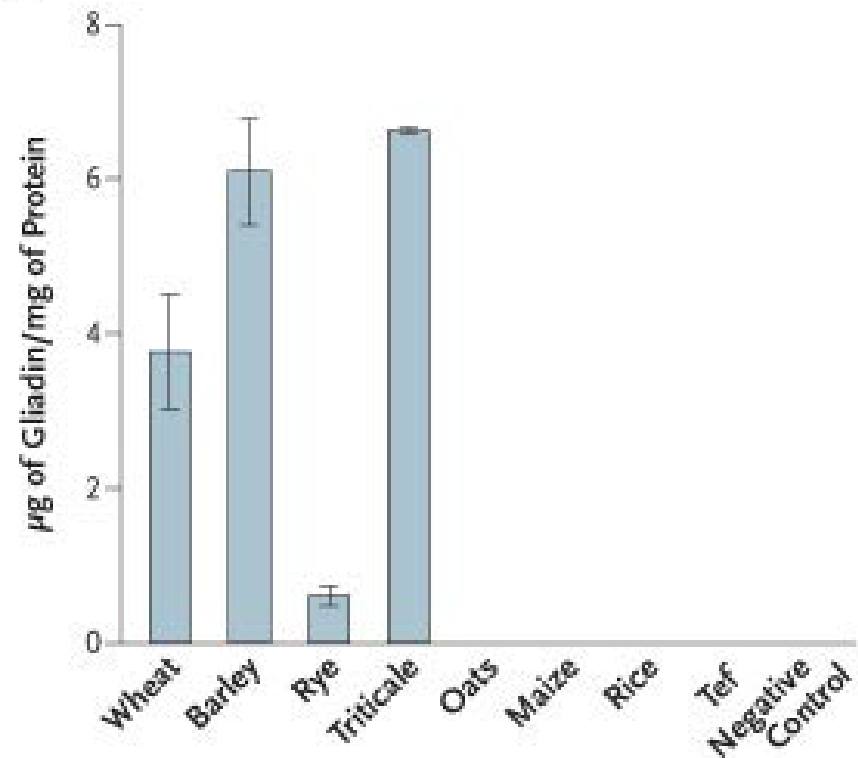


Presence of Immunodominant alpha-gliadin

A

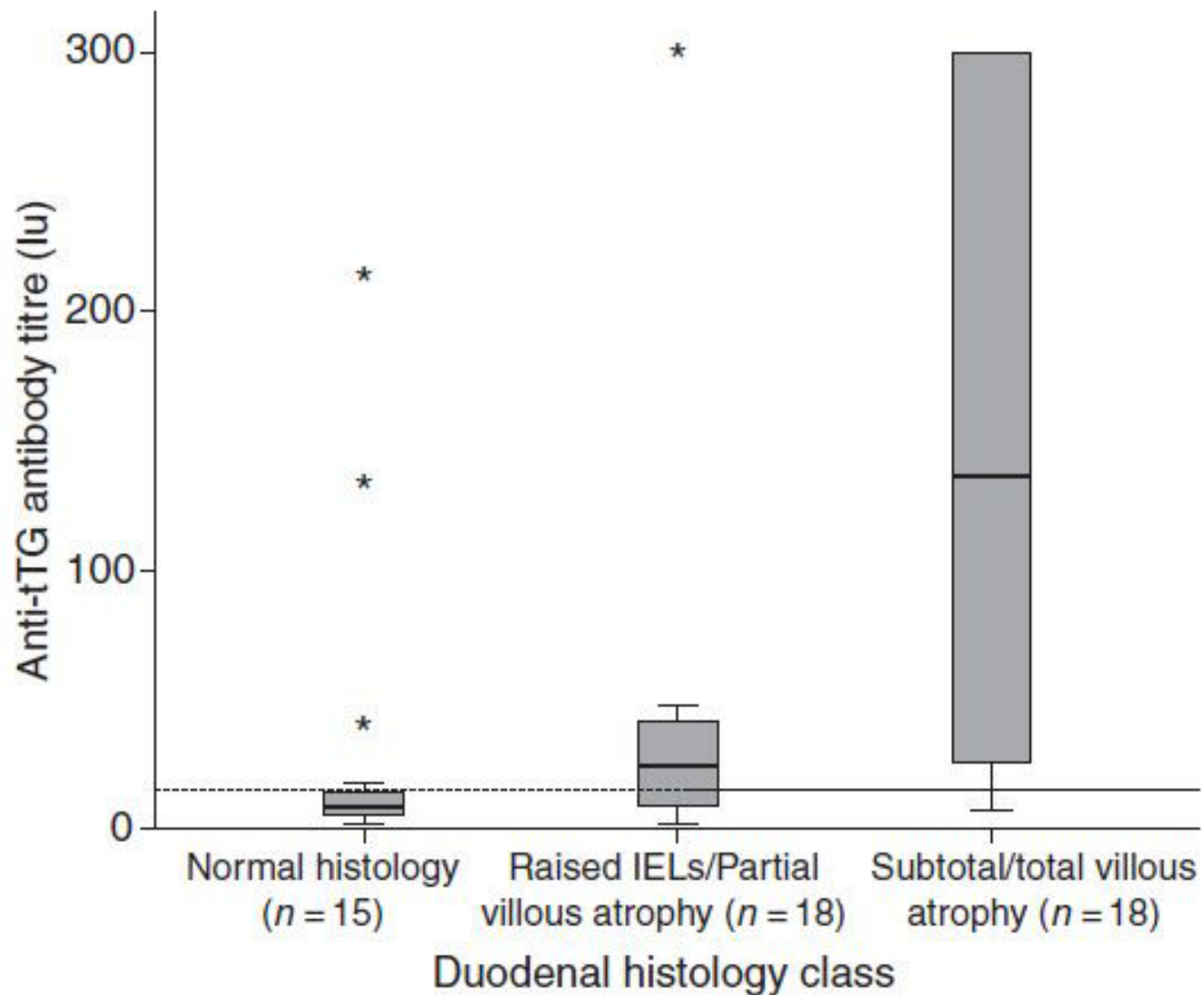


B



Monitoring Dietary Adherence

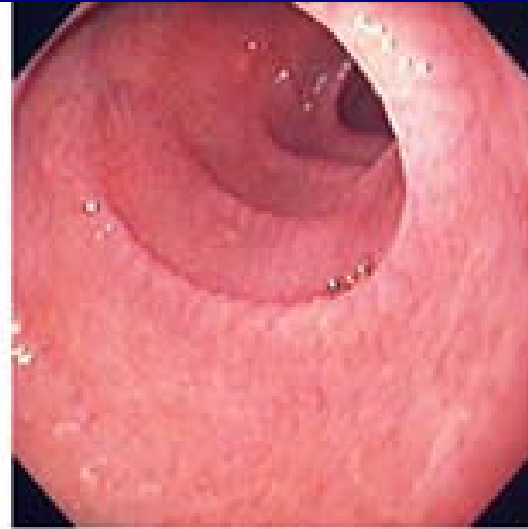
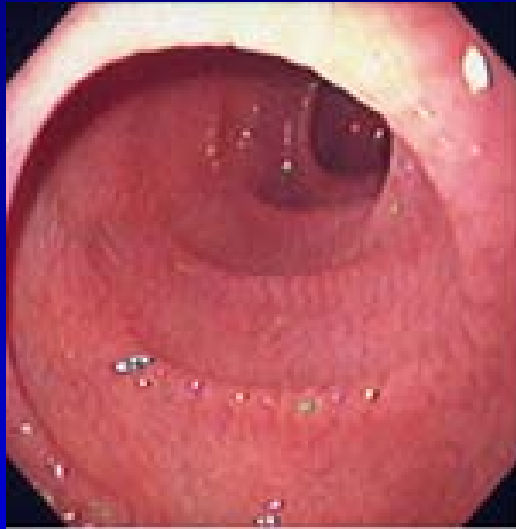
- **Dietary adherence is a challenging issue for many adult and adolescent patients with CD.**
 - Transgressions may occur intentionally or inadvertently because of unknown contamination of food by gluten.
 - Deliberate ingestion may occur because of the excessive cost and poor palatability of a GFD, or secondary to denial, anger or depression related to the diagnosis and consequent dietary restriction
- **There is no simple tool to identify non-adherence to the GFD.**
- **While duodenal biopsy is considered the 'gold standard' for this purpose, frequently repeated biopsies are neither practical nor cost-effective.**



Monitoring Treatment Response

- Long-term follow up study of 158 CD patients mean 15 years
- Repeat biopsy after a minimum of 2 years of a GFD
 - Biopsy normal: 65% Am j. Clin. Path 118(3);459-463
- 39 adults in clinical remission for a mean of 8.5 years on a GFD
 - Normal histology 21%
 - Partial villous atrophy 69%
 - Total villous atrophy 10%

Gastrointest Endo 2003;57(2);181-91



Occult CD in General Practice

- Study of 1200 volunteers in 5 general practices 1999-2001 in South Yorkshire, England
- All screened with AEA and AGA with subsequent small bowel biopsy if positive
- **Prevalence of undiagnosed celiac disease 1%**
 - 3/12 with chronic fatigue dx
 - 3/12 of IBS dx
 - 5/12 with iron deficiency
 - None with chronic diarrhea

**Clinical and laboratory findings in 82
oligosymptomatic Italian children with celiac
disease detected by screening**

Symptom	Percent
Iron deficiency	
With anemia	29
Without anemia	27
Recurrent abdominal pain	24
Mood changes	17
Recurrent aphthous stomatitis	11
Poor appetite	10
Recurrent diarrhea	9
Short stature	7
Abdominal distention	5
Constipation	2
Pubertal delay	2
Hypoalbuminemia	2

Data from: Catassi, C, Fabiani, E, Rätsch, IM, et al, Acta Paediatr 1996; 412(Suppl):29.

Occult CD in General Practice

- Northern Ireland population
- 150 consecutive EGD for various dyspeptic symptoms
 - All received random duodenal biopsies
- Partial or total villous atrophy found in 8/150 cases (5.3%)
- All eight cases were previously undiagnosed CD
- The reported prevalence of CD in N. Ireland is 1/300 vs 16/300 in this study

(Am J. Gastro 1999; 94:231)

Treatment

- “Food Allergen Labeling and Consumer Protection Act” passed 8/2/2004 requires clear labeling of 8 top food allergens by 2006
 - Milk, eggs, soy, wheat, fish, crustacean shellfish, tree nuts, peanuts
 - Requires FDA to issue official rules defining the term “gluten-free” for food labels

Gluten-Free Diets Are Difficult

- Children with CD
 - 72% expressed anger with GFD
 - 69% felt different from peers
 - 61% reported being excluded from activities at school or at friends homes

PRIMARY AMINO ACID SEQUENCE OF A-GLIADIN

1 VRV PVP QLQ P QN P S Q Q Q P Q E Q V P LV Q Q Q Q F L G Q Q Q P F P P Q
41 Q P Y P Q P Q P F P S Q Q P Y L Q L Q P F P Q P Q L P Y S Q P Q P F R P Q Q P Y
81 P Q P Q P Q Y S Q P Q Q P I S Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q I L Q Q I L Q
121 Q Q L I F C M D V V L Q Q H N I A H G R S Q V L Q Q S T Y Q L L Q E L C C Q H L
161 W Q I P E Q S Q C Q A I H N V V H A I L H Q Q Q K Q Q Q Q P S S Q V S F Q Q P
201 L Q Q Y P L G Q G S F R P S Q Q N P Q A Q G S V Q P Q Q L P Q F E E I R N L A L
241 Q T L P A M C N V Y I A P Y C T I A P F G I F G T N

Proline: "P"

Glutamine: "Q"

Extraintestinal Manifestations

- Neuropsychiatric:

- Peripheral Neuropathy: up to 49%, distal, symmetrical, predominantly sensory
- Seizures: 3.5-5.5% prevalence
- Headache/migraines: most common neurologic symptom in children with CD (28% vs 7% controls)
- Depression
- Chronic fatigue
- Anxiety
- Idiopathic cerebellar ataxia
- Cerebral calcifications

Causes of small intestinal villous atrophy other than celiac disease

Bacterial overgrowth

Crohn's disease

Cow's milk protein intolerance (children)

Eosinophilic gastroenteritis

Giardiasis

Lymphoma

Peptic duodenitis

Post gastroenteritis

Tropical sprue

Zollinger-Ellison syndrome

Common variable immunodeficiency

Autoimmune enteropathy

Other immunodeficiency states (usually apparent clinically)

Foods and products that may contain gluten

Frequently overlooked foods that may contain gluten and need to be verified:	NOT ALLOWED in any form:
Brown rice syrup	Wheat (einkorn, durum, faro, graham, kamut, semolina, spelt)
Breading and coating mixes	
Croutons	Rye
Energy bars	Barley
Flour or cereal products	Triticale
Imitation bacon	Malt, malt flavoring, malt vinegar (are generally made from barley, verify the source)
Imitation seafood	
Marinades	
Panko (Japanese bread crumbs)	
Pastas	
Processed luncheon meats	
Sauces, gravies	
Self-basting poultry	
Soy sauce or soy sauce solids	
Soup bases	
Stuffings, dressing	
Thickeners (roux)	
Communion wafers	
Herbal supplements	
Drugs and over-the-counter medications	
Nutritional supplements	
Vitamins and mineral supplements	
Play-dough, crayons, paint, glue, paper mache: A potential problem if the child puts their hands on or in the mouth while playing. Wash hands after using these products.	